The respiratory system serves to supply sufficient oxygen to meet metabolic demands and remove carbon dioxide. Abnormalities in any of the multiple processes (including ventilation, perfusion, and diffusion) that are involved in tissue oxygenation and carbon dioxide removal can lead to respiratory failure. The pathophysiologic manifestations of respiratory disease processes are profoundly influenced by age- and growth-dependent changes in the physiology and anatomy of the respiratory control mechanisms, airway dynamics, and lung parenchymal characteristics. Smaller airways, a more compliant chest wall, and poor hypoxic drive render a younger infant more vulnerable compared to an older child with similar severity of disease.

Respiratory distress may be diagnosed from signs such as cyanosis, nasal flaring, grunting, tachypnea, wheezing, chest wall retractions, and stridor. Respiratory failure can be present without respiratory distress; a patient with abnormalities of central nervous system (CNS) or neuromuscular disease or exhaustion might not be able to mount sufficient effort to appear in respiratory distress. A child who appears in respiratory distress might not have a respiratory illness; a patient with primary metabolic acidosis (diabetic ketoacidosis) or CNS excitatory states (encephalitis) can present in severe respiratory distress without respiratory disease.

Bibliography is available at Expert Consult.

### 373.1 Lung Volumes and Capacities in Health and Disease

Traditionally, lung volumes are measured with a spirogram (Fig. 373-1). **Tidal volume** \( (V_T) \) is the amount of air moved in and out of the lungs during each breath; at rest, \( V_T \) is normally 6-7 mL/kg body weight. **Inspiratory capacity** is the amount of air inspired by maximum inspiratory effort after tidal expiration. **Expiratory reserve volume** is the amount of air exhaled by maximum expiratory effort after tidal expiration. The volume of gas remaining in the lungs after maximum expiration is **residual volume**. **Vital capacity** is defined as the amount of air moved in and out of the lungs with maximum inspiration and expiration. Vital capacity, inspiratory capacity, and expiratory reserve volume are decreased in lung pathology but are also effort dependent. **Total lung capacity** is the volume of gas occupying the lungs after maximum inspiration.

**Flow volume relationship** offers a valuable means at the bedside or in an office setting to detect abnormal pulmonary mechanics and response to therapy with relatively inexpensive and easy-to-use devices. After maximum inspiration, the patient forcefully exhales through a mouthpiece into the device until residual volume is reached followed by maximum inspiration (Fig. 373-2). Flow is plotted against volume. **Maximum forced expiratory flow** \( (\text{FEF}_{\text{max}}) \) is generated in the early part of exhalation, and it is a commonly used indicator of airway obstruction in asthma and other obstructive lesions. Provided maximum pressure is generated consistently during exhalation, a decrease in flow is a reflection of increased airway resistance. The total volume exhaled during this maneuver is **forced vital capacity** \( (\text{FVC}) \). Volume exhaled in 1 sec is referred to as \( \text{FEV}_1 \). \( \text{FEV}_1/\text{FVC} \) is expressed as a percentage.
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Figure 373-2 Flow volume loop in a normal person performed after maximal inspiration followed by forced complete expiration and forced complete inhalation. FEF_max represents maximum flow during expiration. This is attained soon after initiation of the expiration. Fall in expiratory flow is gradual until it reaches zero after exhalation is complete. FEF_{25%-75%} represents mean flow from 25% (FEF_{25%}) to 75% (FEF_{75%}) of exhaled forced expiratory volume (FEV), also termed forced vital capacity (FVC). FEV_{1} is amount of volume after 1 sec of forced exhalation. Normally FEV_{1} is around 80% of FVC.

Figure 373-3 Flow volume loops in intrapulmonary airway obstruction and restrictive disorders. Note that in intrapulmonary airway obstruction, there is a decrease in FEF_max, FEF_{25%-75%}, and FEV_{1}/FVC. The middle part of expiratory loop appears concave. In restrictive disorder, the flow volume loop assumes a more vertically oblong shape compared to normal. Changes in shape of the flow volume loop and individual values depend on the type of disease and the extent of severity. Serial determinations provide valuable information regarding disease evolution and response to therapy.

Functional residual capacity (FRC) is the amount of air left in the lungs after tidal expiration. FRC has important pathophysiologic implications. Alveolar gas composition changes during inspiration and expiration. Alveolar Po_{2} (PAo_{2}) increases and alveolar Pco_{2} (PACo_{2}) decreases during inspiration as fresh atmospheric gas enters the lungs. During exhalation, PAo_{2} decreases and PACo_{2} increases as pulmonary capillary blood continues to remove oxygen from and add CO_{2} into the alveoli (Fig. 373-4). FRC acts as a buffer, minimizing the changes in PAo_{2} and PACo_{2} during inspiration and expiration. FRC represents the environment available for pulmonary capillary blood for gas exchange at all times.

A decrease in FRC is often encountered in alveolar interstitial diseases and thoracic deformities. The major pathophysiologic consequence of decreased FRC is hypoxemia. Reduced FRC results in a sharp decline in PAo_{2} during exhalation because a limited volume is available for gas exchange. P_{02} of pulmonary capillary blood therefore falls excessively during exhalation, leading to a decline in arterial Po_{2} (PAo_{2}). Any increase in PAo_{2} (and therefore Pao_{2}) during inspiration cannot compensate for the decreased Pao_{2} during expiration. The explanation for this lies in the shape of O_{2}-hemoglobin (Hb) dissociation curve, which is sigmoid shaped (Fig. 373-5). Because most of the oxygen in blood is combined with Hb, it is the percentage of oxyhemoglobin (So_{2}) that gets averaged rather than the P_{O_{2}}. Although an
During expiration, the opposite changes occur as pulmonary capillary blood continues to remove O₂ and add CO₂ from the alveoli without atmospheric enrichment. Note that during the early part of inspiration, alveolar PₐO₂ continues to fall and PCO₂ continues to rise because of inspiration of the dead space that is occupied by the previously exhaled gas. (Modified from Comroe JH: Physiology of respiration, ed 2, Chicago, 1974, Year Book Medical Publishers, p 12.)

**Figure 373-4** Alveolar PₐO₂ rises and PₐCO₂ falls during inspiration as fresh atmospheric gas is brought into the lungs. During expiration, the opposite changes occur as pulmonary capillary blood continues to remove O₂ and add CO₂ from the alveoli without atmospheric enrichment. Note that during the early part of inspiration, alveolar PₐO₂ continues to fall and PCO₂ continues to rise because of inspiration of the dead space that is occupied by the previously exhaled gas. (Modified from Comroe JH: Physiology of respiration, ed 2, Chicago, 1974, Year Book Medical Publishers, p 12.)

**Figure 373-5** Oxygen-hemoglobin dissociation curve. PₐO₂ of adult blood is around 27 torr. Under basal conditions, mixed venous blood has PₐO₂ of 40 torr and oxygen-hemoglobin saturation of 75%. In arterial blood, these values are 100 torr and 97.5%, respectively. Note that there is a steep decline in oxygen-hemoglobin saturation at PₐO₂ <50 torr, but relatively little increase in saturation is gained at PₐO₂ >70 torr.

**Figure 373-6** Lung compliance is significantly influenced by the functional residual capacity (FRC). The same change in pressure is associated with less change in volume when FRC is abnormally decreased (a) or abnormally increased (c) compared to the normal state (b). FRC. Abnormalities of FRC result in increased work of breathing with spontaneous respiration and increased barotrauma in mechanical ventilation.

**373.2 Chest Wall**

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The chest wall and diaphragm of an infant are mechanically disadvantaged compared to that of an adult when required to increase thoracic (and therefore the lung) volume. The infant's ribs are oriented much more horizontally and the diaphragm is flatter and less domed. Consequently, the infant is unable to duplicate the efficiency of upward and outward movement of obliquely oriented ribs and downward displacement of the domed diaphragm in an adult to expand the thoracic capacity. Additionally, the infant's rib cage is softer and thus more compliant compared to an adult's rib cage. Although a soft, highly compliant chest wall is beneficial to a baby in its passage through the birth canal and allows future lung growth, it places the young infant in a vulnerable situation under certain pathologic conditions. Chest wall compliance is a major determinant of FRC. Because the chest wall and the lungs recoil in opposite directions at rest, FRC is reached at the point where the outward elastic recoil of the thoracic cage counterbalances the inward lung recoil. This balance is attained at a lower lung volume in a young infant because of the extremely high thoracic compliance compared to older children (Fig. 373-7). The measured FRC in infants is higher than expected because respiratory muscles of infants maintain the thoracic cage in an inspiratory position at all times. Additionally, some amount of air trapping during expiration occurs in young infants.

The increased chest wall compliance is a distinct disadvantage to the young infant under several pathologic conditions. A decrease in muscle tone, as occurs in rapid eye movement (REM) sleep or with CNS depression, allows greater chest wall retraction because of less opposition to the lung recoil; the FRC decreases in such states. The respiratory muscles of infants are poorly equipped to sustain large workloads. They are more easily fatigued than those of older children, limiting their ability to maintain adequate ventilation in lung disease. In diseases of poor lung compliance (atelectasis, pulmonary edema), excessive lung recoil results in greater retraction of the soft chest wall and more loss of FRC than occurs in older children and adults with stiffer chest walls. Increased negative intrathoracic pressure required to overcome airway resistance in upper airway obstruction also produces greater chest wall...
Bibliography
The elastic recoil of a relatively more compliant chest wall is balanced by the lung recoil at a lower volume (FRC) in infants compared to adults. FRC, functional residual capacity.

Figure 373-7 Schematic of interaction between chest wall and lung recoil in infants compared to adults. The elastic recoil of a relatively more compliant chest wall is balanced by the lung recoil at a lower volume (FRC) in infants compared to adults. FRC, functional residual capacity.

recoil and reduced FRC in young infants. Application of PEEP is beneficial in such states for stabilizing the chest wall and restoring FRC.

Young infants do not tolerate sustained respiratory loads as well as older children and adults. Respiratory muscle ontogeny is characterized by changes in the composition of muscle fiber types in the diaphragm and intercostals throughout infancy. Type I fibers are slow-twitch and high-oxidative in nature, whereas type II fibers are fast-twitch and low-oxidative. Type I fibers have low contractility but are fatigue resistant. Type II fibers have high contractility but are more prone to fatigue. The proportion of type I fibers in the diaphragm and intercostals of premature infants is only about 10%. This increases to around 25% in full-term newborns and around 50% in children older than age 2 yr. Respiratory muscles of premature babies and young infants are therefore more susceptible to fatigue, resulting in earlier decompensation.

Abnormalities of the chest wall are encountered in certain pathologic conditions. Chest wall instability can result from trauma (fractured ribs, thoracotomy) and neuromuscular diseases that lead to intercostal and diaphragmatic muscle weakness. The increased chest wall compliance makes such children more vulnerable to respiratory decompensation when faced with similar pulmonary pathology compared to older children and adults with stiffer chest walls. Children with rigid, noncompliant chest wall (asphyxiating thoracic dystrophy of Jeune [see Chapters 417.3 and 700], achondroplasia [see Chapter 417.4]) have markedly diminished lung volumes and capacities.

Bibliography is available at Expert Consult.

373.3 Pulmonary Mechanics and Work of Breathing in Health and Disease

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The movement of air in and out of the lungs requires a sufficient pressure gradient between alveoli and atmosphere during inspiration and expiration. Part of the pressure gradient is required to overcome the lung and chest wall elastic; another part is needed to overcome airway resistance. Elastance refers to the property of a substance to oppose deformation or stretching. It is calculated as a change in pressure (ΔP) divided by change in volume (ΔV). Elastic recoil is a property of a substance that enables it to return to its original state after it is no longer subjected to pressure. Compliance (ΔV / ΔP) is the reciprocal of elastance. In the context of the pulmonary parenchyma, airways, and the chest wall, the compliance refers to their distensibility. Resistance is calculated as the amount of pressure required to generate flow of gas across the airways. Resistance to laminar flow is governed by Poiseuille's law stated as:

\[ R = \frac{8\eta \rho v}{\pi r^4} \]

where \( R \) is resistance, \( l \) is length, \( \eta \) is viscosity, and \( r \) is the radius. The practical implication of pressure-flow relationship is that airway resistance is inversely proportional to its radius raised to the 4th power. If the airway lumen is decreased by half, the resistance increases 16-fold. Newborns and young infants with their inherently smaller airways are especially prone to marked increase in airway resistance from inflamed tissues and secretions. In diseases in which airway resistance is increased, flow often becomes turbulent. Turbulence depends to a great extent on the Reynolds number (Re), a dimensionless entity, which is calculated as:

\[ Re = \frac{2rvd + \eta}{\eta} \]

where \( r \) is radius, \( v \) is velocity, \( d \) is density, and \( \eta \) is viscosity. Turbulence in gas flow is most likely to occur when Re exceeds 2000. Resistance to turbulent flow is greatly influenced by density. A low-density gas such as helium-oxygen mixture decreases turbulence in obstructive airway diseases such as viral laryngotracheobronchitis and asthma. Neonates and young infants are predominantly nose breathers and therefore even a minimal amount of nasal obstruction is poorly tolerated.

The diaphragm is the major muscle of respiration. When additional work of breathing (WOB) is required, intercostal and other accessory muscles of respiration also contribute to the increased work. The \( V_t \) and respiratory rate are adjusted, both in health and disease, to maintain the required minute volume with the least amount of energy expenditure. The total WOB (necessary to create pressure gradients to move air) is divided into 2 parts. The first part is to overcome the lung and chest wall elastic and is referred to as elastic work (\( W_{\text{elast}} \)). The second part is to overcome airway and tissue resistance, and is referred to as resistive work (\( W_{\text{resist}} \)). \( W_{\text{elast}} \) is directly proportional to \( V_t \), whereas \( W_{\text{resist}} \) is determined by the rate of airflow and, therefore, the respiratory rate. The total WOB is lowest at a rate of 35-40/min for neonates and 14-16/min for older children and adults. \( W_{\text{elast}} \) is disproportionately increased in diseases with decreased compliance and \( W_{\text{resist}} \) is increased in airway obstruction. Consequently, respirations are shallow (low \( V_t \)) and rapid in diseases of low compliance and deep and relatively slow (low flow rate) in diseases of increased resistance.

Compared to older children, young infants have disproportionately greater \( W_{\text{elast}} \) because the negative intrapleural pressure during inspiration causes the retractive (more compliant) chest wall to collapse and pose an impediment to air entry. Young infants increase their respiratory rate with any mechanical abnormality. Other examples of compliant chest wall being a disadvantage include flail chest resulting from...
Bibliography
rib fractures, thoracotomy, and neuromuscular weakness. One of the salutary effects of continuous positive airway pressure in such situations is the stabilization of the chest wall. Under normal conditions, the energy cost of WOB contributes to only approximately 2% of total caloric expenditure. In children with chronic lung disease or congestive heart failure the WOB can contribute to as much as 40% of total energy expenditure during physical activity, thus increasing their caloric needs.

**Time constant**, measured in seconds, is a product of compliance and resistance. It is a reflection of the amount of time required for proximal airway pressure (and therefore volume) to equilibrate with alveolar pressure. It takes 3 time constants for 95%, and 5 time constants for 99% of pressure equilibration to occur. Because intrathoracic airways expand during inspiration and narrow during expiration, expiratory time constant is longer than inspiratory time constant. Diseases characterized by decreased compliance (pneumonia, pulmonary edema, atelectasis) are associated with a shorter time constant and therefore require less time for alveolar inflation and deflation. Diseases associated with increased resistance (asthma, bronchiolitis, aspiration syndromes) have prolonged time constant and therefore require more time for alveolar inflation and deflation. Pathologic alterations in time constants have practical significance during mechanical ventilation. Patients with shorter time constants are best ventilated with relatively smaller tidal volumes and faster rates to minimize peak inflation pressure. In patients with increased airway resistance, a fast respiratory rate (and, therefore, less time) does not allow enough pressure equilibration to occur between the proximal airway and the alveoli. Inadequate inspiratory time results in lower VT, whereas insufficient exhalation (and, therefore, less time) does not allow enough pressure equilibration to occur. In patients with increased airway resistance, a fast respiratory rate and larger tidal volumes.

Because the trachea and airways of an infant are much more compliant than those of older children and adults, changes in intrapleural pressure result in much greater changes in airway diameter. The airway can be divided into 3 anatomic parts: the extrathoracic airway extends from the nose to the thoracic inlet, the intrathoracic–extrapulmonary airway extends from the thoracic inlet to the main stem bronchi, and the intrapulmonary airway is within the lung parenchyma. During normal respirations, intrathoracic airways expand in inspiration as intrapleural pressure becomes more negative and narrow in expiration as they return to their baseline at FRC. The changes in diameter are of little significance in normal respiration. In diseases characterized by airway obstruction, much greater changes in intrapleural pressure are required to generate adequate airflow, resulting in greater changes in airway lumen. The changes in the size of airway during respiration are accentuated in young infants with their softer, more compliant airways.

In extrathoracic airway obstruction (choanal atresia [see Chapter 376], retropharyngeal abscess, laryngotracheobronchitis [see Chapter 385]), the high negative intrapleural pressure during inspiration is transmitted up to the site of obstruction, after which there is a rapid dissipation of pressure. Therefore, the extrathoracic airway below the site of obstruction has markedly increased negative pressure inside, resulting in its collapse, which makes the obstruction worse (Fig. 373-8A). This produces inspiratory difficulty, prolongation of inspiration, and inspiratory stridor. Also, the increased negative intrapleural pressure results in chest wall retractions. During expiration, the increased positive intrapleural pressure is again transmitted up the airways to the site of obstruction, leading to a distention of the extrathoracic airway and amelioration of obstruction (Fig. 373-8B).

Because of the increased positive intrapleural pressure during expiration, the chest wall tends to bulge out, which produces the classic paradoxical respiration, in which the chest retracts during inspiration and bulges out during expiration. The younger the child, the softer is the chest wall and the more marked is the paradoxical respiration of extrathoracic airway obstruction. A pattern of seeseaw respiration may also be evident in newborns and young infants as the compliant chest wall is sucked in and the abdomen bulges out during inspiration, with the converse happening during expiration.

In obstruction of intrathoracic–extrapulmonary airway (vascular ring [see Chapter 386.8], mediastinal tumors) and intrapulmonary airway (asthma, bronchiolitis), the increased negative intrapleural pressure results in a distention of intrathoracic airways during inspiration, thus providing some relief from obstruction (Fig. 373-9A).

During expiration, the increased positive intrathoracic pressure is transmitted up to the site of obstruction, after which it dissipates rapidly. The intrathoracic airway above the site of obstruction is

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**Figure 373-8** A, In extrathoracic airway obstruction, the increased negative pressure during inspiration is transmitted up to the site of obstruction. This results in collapse of the extrathoracic airway below the site of obstruction, making the obstruction worse during inspiration. Note that the pressures are compared to the atmospheric pressure, which is traditionally represented as 0 cm. Terminal airway pressure is calculated as intrapleural pressure plus lung recoil pressure. Lung recoil pressure is arbitrarily chosen as 5 cm for the sake of simplicity. B, During expiration, the positive pressure below the site of obstruction results in distention of extrathoracic airway and amelioration of symptoms.
Bibliography
tion of expiration, and expiratory wheezing. Any airway obstruction within the thorax results in expiratory wheezing.

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373.5 Interpretation of Clinical Signs to Localize the Site of Pathology

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The first step in establishing the diagnosis of respiratory disease is appropriate interpretation of clinical findings. Respiratory distress can occur without respiratory disease, and severe respiratory failure can be present without significant respiratory distress. Diseases characterized by CNS excitation, such as encephalitis, and neuroexcitatory drugs are
Bibliography
extrathoracic airway obstruction. Expiratory **wheezing** is characteristic of intrathoracic airway obstruction, either extrapulmonary or intrapulmonary. **Grunting** is produced by expiration against a partially closed glottis and is an attempt to maintain positive airway pressure during expiration for as long as possible. Such prolongation of positive pressure is most beneficial in alveolar diseases that produce widespread loss of FRC, such as in pulmonary edema, hyaline membrane disease, and pneumonia. Grunting is also effective in small airway obstruction (bronchiolitis) to maintain a higher positive pressure in the airway during expiration, decreasing the airway collapse.

**Bibliography is available at Expert Consult.**

### 373.6 Ventilation-Perfusion Relationship in Health and Disease

*Ashok P. Samaik, Sabrina M. Heidemann, and Jeff A. Clark*

Gravitational force pulls the lung away from the nondependent part of the parietal pleura. Therefore, alveoli and airways in the nondependent

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**Table 373-1 Interpreting the Clinical Signs of Respiratory Disease**

<table>
<thead>
<tr>
<th>SIGN</th>
<th>EXTRATHORACIC AIRWAY OBSTRUCTION</th>
<th>INTRATHORACIC–EXTRAPULMONARY AIRWAY OBSTRUCTION</th>
<th>INTRAPULMONARY AIRWAY OBSTRUCTION</th>
<th>PARENCHYMAL PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachypnea</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Retractions</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Stridor</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Wheezing</td>
<td>±</td>
<td>+++</td>
<td>++++</td>
<td>±</td>
</tr>
<tr>
<td>Grunting</td>
<td>±</td>
<td>±</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

**Figure 373-11 Presentation profiles of respiratory failure in childhood.** When a mechanical dysfunction is present (by far, the most common circumstance), arterial hypoxemia and hypercapnia (and hence, pH) are sensed by peripheral (carotid bodies) and central (medullary) chemoreceptors. After being integrated with other sensory information from the lungs and chest wall, chemoreceptor activation triggers an increase in the neural output to the respiratory muscles (vertical arrows), which results in the physical signs that characterize respiratory distress. When the problem resides with the respiratory muscles (or their innervation), the same increase in neural output occurs (arrow), but the respiratory muscles cannot increase their effort as demanded; therefore, the physical signs of distress are more subtle. Finally, when the control of breathing is itself affected by disease, the neural response to hypoxemia and hypercapnia is absent or blunted and the gas exchange abnormalities are not accompanied by respiratory distress.
Bibliography

Gas Exchange in Health and Disease

The main function of the respiratory system is to remove carbon dioxide from and add oxygen to the systemic venous blood brought to the lung. The composition of the inspired gas, ventilation, perfusion, diffusion, and tissue metabolism have a significant influence on the arterial blood gases.

The total pressure of the atmosphere at sea level is 760 torr. With increasing altitude, the atmospheric pressure decreases. The total atmospheric pressure is equal to the sum of partial pressures exerted by each of its component gases. Alveolar air is 100% humidified and, therefore, for alveolar gas calculations, the inspired gas is also presumed to be 100% humidified. At a temperature of 37°C (98.6°F) and 100% humidity, water vapor exerts pressure of 47 torr, regardless of altitude. In a natural setting, the atmosphere consists of 20.93% oxygen.

Partial pressure of oxygen in inspired gas (P\text{O}_2) at sea level is therefore (760−47)×20.93% = 149 torr. When breathing 40% oxygen at sea level, P\text{O}_2 is (760−47)×40% = 285 torr. At higher altitudes, breathing different concentrations of oxygen, P\text{O}_2 is less than at sea level, depending on the prevalent atmospheric pressures. In Denver (altitude of 5,000 feet and barometric pressure of 632 torr), P\text{O}_2 in room air is (632−47)×20.93% = 122 torr, and in 40% oxygen, it is (632−47)×40% = 234 torr.

Minute volume is a product of V\text{T} and respiratory rate. Part of the V\text{T} occupies the conducting airways (anatomic dead space), which does not contribute to gas exchange in the alveoli. Alveolar ventilation is the volume of atmospheric air entering the alveoli and is calculated as (V\text{T}−dead space)×respiratory rate. Alveolar ventilation is inversely proportional to arterial P\text{CO}_2 (P\text{aCO}_2). When alveolar ventilation is halved, P\text{aCO}_2 is doubled. Conversely, doubling of alveolar ventilation decreases P\text{aCO}_2 by 50%. Alveolar P\text{O}_2 (P\text{aO}_2) is calculated by the alveolar air equation as follows:

\[
P\text{aO}_2 = P\text{O}_2 − (P\text{aCO}_2 × R)
\]

where R is the respiratory quotient. For practical purposes, P\text{aCO}_2 is substituted by arterial P\text{CO}_2 (P\text{aCO}_2) and R is assumed to be 0.8. According to the alveolar air equation, for a given P\text{O}_2, a rise in P\text{aCO}_2 of 10 torr results in a decrease in P\text{aO}_2 by 10÷0.8 or 10×1.25 or 12.5 torr. Thus, proportionately inverse changes in P\text{aO}_2 occur to the extent of 1.25×the changes in P\text{aCO}_2 (or P\text{aCO}_2).

After the alveolar gas composition is determined by the inspired gas conditions and process of ventilation, gas exchange occurs by the process of diffusion and equilibration of alveolar gas with pulmonary capillary blood. Diffusion depends on the alveolar capillary barrier and the amount of available time for equilibration. In health, the equilibration of alveolar gas and pulmonary capillary blood is complete for both oxygen and carbon dioxide. In diseases in which alveolar capillary barrier is abnormally increased (alveolar interstitial diseases) and/or when the time available for equilibration is decreased (increased blood flow velocity), diffusion is incomplete. Because of its greater solubility in liquid medium, carbon dioxide is 20 times more diffusible than oxygen. Therefore, diseases with diffusion defects are characterized by marked alveolar-arterial oxygen (A−aO)_2 gradients and hypoxemia. Significant elevation of CO_2 does not occur as a result of a diffusion defect unless there is coexistent hypoventilation.

Venous blood brought to the lungs is “arterialized” after diffusion is complete. After complete arterialization, the pulmonary capillary blood should have the same P\text{O}_2 and P\text{aCO}_2 as in the alveoli. The arterial blood gas composition is different from that in the alveoli, even in normal conditions because there is a certain amount of dead space ventilation as well as venous admixture in a normal lung. Dead space ventilation results in a higher P\text{aCO}_2 than P\text{aCO}_2, whereas venous admixture or right-to-left shunting results in a lower P\text{aO}_2, compared to the alveolar gas composition (see Fig. 373-12). P\text{ao2} is a reflection of the amount of oxygen dissolved in blood, which is a relatively minor component of total blood oxygen content. For every 100 torr P\text{O}_2, there is 0.3 mL of dissolved O\text{2} in 100 mL of blood. The total blood oxygen...
Bibliography
content is composed of the dissolved oxygen and the oxygen bound to hemoglobin. Each gram of hemoglobin carries 1.34 mL of O₂ when 100% saturated with oxygen. Thus, 15 g of hemoglobin carries 20.1 mL of oxygen. **Arterial oxygen content (CaO₂)**, expressed as mL O₂/dL blood, can be calculated as \((\text{PaO}_2 \times 0.003) + (\text{Hb} \times 1.34 \times \text{So}_2)\), where Hb is grams of Hb per deciliter of blood and So₂ is percentage of oxyhemoglobin saturation. The relationship of Po₂ and the amount of oxygen carried by the hemoglobin is the basis of the O₂-Hb dissociation curve (see Fig. 373-5). The Po₂ at which hemoglobin is 50% saturated is referred to as P₅₀. At a normal pH, hemoglobin is 94% saturated at Po₂ of 70, and little further gain in saturation is accomplished at a higher Po₂. At Po₂ <50, there is a steep decline in saturation and therefore the oxygen content.

Oxygen delivery to the tissues is a product of oxygen content and cardiac output. When hemoglobin is near 100% saturated, the blood contains approximately 20 mL oxygen per 100 mL or 200 mL/L. In a healthy adult, the cardiac output is approximately 5 L/min, oxygen delivery 1,000 mL/min, and oxygen consumption 250 mL/min. Mixed venous blood returning to the heart has a Po₂ of 40 torr and is 75% saturated with oxygen. Blood oxygen content, cardiac output, and oxygen consumption are important determinants of mixed venous oxygen saturation. Given a steady-state blood oxygen content and oxygen consumption, the mixed venous saturation is an important indicator of cardiac output. A declining mixed venous saturation in such a state indicates decreasing cardiac output.

Bibliography is available at Expert Consult.

### 373.8 Interpretation of Blood Gases

**Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark**

Clinical observations and interpretation of blood gas values are critical in localizing the site of the lesion and estimating its severity (Table 373-2). In airway obstruction above the carina (subglottic stenosis, vascular ring), blood gases reflect overall alveolar hypoventilation. This is manifested by an elevated Paco₂ and a proportionate decrease in PaO₂ as determined by the alveolar air equation. A rise in PaCO₂ of 20 torr decreases PaO₂ by 20 × 1.25 or 25 torr. In the absence of significant parenchymal disease and intrapulmonary shunting, such lesions respond very well to supplemental oxygen in reversing hypoxemia. Similar blood gas values, demonstrating alveolar hypoventilation and response to supplemental oxygen, are observed in patients with a depressed respiratory center and ineffective neuromuscular function, resulting in respiratory insufficiency. Such patients can be easily distinguished from those with airway obstruction by their poor respiratory effort.

In intrapulmonary airway obstruction (asthma, bronchiolitis), blood gases reflect ventilation-perfusion imbalance and venous admixture. In these diseases, the obstruction is not uniform throughout the lungs, resulting in areas that are hyperventilated and others that are hypoventilated. Pulmonary capillary blood coming from hyperventilated areas has a higher Pao₂ and lower Pco₂, whereas that coming from hypoventilated regions has a lower Pao₂ and higher Pco₂. A lower blood Pco₂ can compensate for the higher Pco₂ because the Hb-CO₂ dissociation curve is relatively linear. In mild disease, the hyperventilated areas predominate, resulting in hypocarbia. An elevated Pao₂ in hyperventilated areas cannot compensate for the decreased Pao₂ in hypoventilated areas because of the shape of the O₂-Hb dissociation curve. This results in venous admixture, arterial desaturation, and decreased Pao₂ (see Fig. 373-12). With increasing disease severity, more areas become hypoventilated, resulting in normalization of Paco₂ with a further decrease in Pao₂. A normal or slightly elevated Paco₂ in asthma should be viewed with concern as a potential indicator of impending respiratory failure. In severe intrapulmonary airway obstruction, hypoventilated areas predominate, leading to hypercapnia, respiratory acidosis, and hypoxemia. The degree to which supplemental oxygenation raises Pao₂ depends on the severity of the illness and the degree of venous admixture.

In alveolar and interstitial diseases, blood gas values reflect both intrapulmonary right-to-left shunting and a diffusion barrier. Hypoxemia is a hallmark of such conditions occurring early in the disease process. Paco₂ is either normal or decreased. An increase in Paco₂ is observed only later in the course, as muscle fatigue and exhaustion result in hyperventilation. Response to supplemental oxygen is relatively poor with shunting and diffusion disorders compared to other lesions. Most clinical entities present with mixed lesions. A child with a vascular ring might also have an area of atelectasis; the arterial blood gas reflects both processes. The blood gas values reflect the more dominant lesion.

Bibliography is available at Expert Consult.

### 373.9 Pulmonary Vasculature in Health and Disease

**Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark**

The tunica media of the pulmonary arteries of the fetus become more muscular in the last trimester of pregnancy (see Chapter 101.1). Up to 90% of the systemic venous return is shunted away from the pulmonary arterial circulation to the systemic arterial circulation through the foramen ovale and the ductus arteriosus. After birth, with functional closure of the foramen ovale and the ductus arteriosus, and dilation of the pulmonary arterial circulation with consequent decrease in pulmonary vascular resistance (PVR), all of the right ventricular output passes through the lung. The PVR is approximately 50% of the systemic arterial resistance 3 days after birth. In the next several wk after birth as pulmonary arterial musculature in the tunica media involutes, there is a further decline in PVR and therefore in pulmonary artery pressure. Two to 3 mo after birth, the PVR and the pulmonary artery pressure

<table>
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<tr>
<th>Table 373-2 Interpretation of Arterial Blood Gas Values</th>
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<td><strong>LESION</strong></td>
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<td>Central (above the carina) airway obstruction, or Depressed respiratory center, or Ineffective neuromuscular function</td>
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<td>Intrapulmonary airway obstruction</td>
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<td>Alveolar–interstitial pathology</td>
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ABG, arterial blood gas; V/Q , ventilation-perfusion.
Bibliography
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are approximately 15% of the systemic values, a relationship that exists through childhood and adolescence. Pulmonary vasculature constricts in response to hypoxemia, acidosis, and hypercarbia and dilates with increased alveolar and arterial $P_O_2$, alkalosis, and hypocarbia. Younger infants, with their relatively muscular pulmonary arteries, are especially susceptible to pulmonary vasoconstrictive stimuli.

Failure of the pulmonary arterial circulation to dilate after birth results in persistent pulmonary hypertension of the newborn (see Chapter 101.7). Because of the persistently high PVR, the systemic venous blood returning to the right side of the heart continues to be shunted across the foramen ovale and the ductus arteriosus to the systemic arterial circulation, leading to a vicious cycle of hypoxemia, acidosis, and further pulmonary vasoconstriction.

The relatively high PVR opposes excessive left-to-right shunting in full-term neonates with ventricular septal defect and patent ductus arteriosus (see Chapter 426). Such infants do not usually manifest heart failure until 2-3 mo after birth, when PVR has sufficiently declined. Premature infants who have lesions capable of left-to-right shunting are susceptible to developing heart failure earlier in life because of less musculature in pulmonary artery tunica media and, therefore, a lower PVR. The gradual physiologic decline in PVR over the 1st 2-3 mo of life also explains how infants with anomalous left coronary artery arising from the pulmonary artery are asymptomatic at birth but present with signs of coronary insufficiency when PVR has fallen sufficiently to critically decrease coronary perfusion. Persistent and long-term left-to-right shunting carries the risk of developing secondary pulmonary vascular disease characterized by the postnatal development of medial muscular hypertrophy followed by intimal proliferation and increased PVR. Early changes in pulmonary vasculature are reversible with correction of the congenital heart defect responsible for left-to-right shunting. Advanced pulmonary vascular disease is characterized by irreversible intimal and medial changes. When PVR is increased to suprasystemic levels, right-to-left shunting occurs and is characterized by a cyanotic state (Eisenmenger syndrome), making the heart defect inoperable in the absence of an accompanying lung transplantation (see Chapter 433.2).

**Pulmonary hypertension** can develop without a well-defined etiology (primary pulmonary hypertension) or as a consequence of an underlying disease (secondary pulmonary hypertension) (see Chapter 433). Adverse effects of pulmonary hypertension are related to an increased right ventricular afterload, decreased cardiac output, and heart failure characterized by increased systemic venous pressure, hepatomegaly, and edema. In an acute situation, right ventricular failure and decreased cardiac output can worsen oxygen delivery and hypoxemia. Right ventricular failure secondary to pulmonary pathology is referred to as cor pulmonale. Secondary pulmonary hypertension is a common occurrence in end-stage chronic obstructive pulmonary disease such as cystic fibrosis (see Chapter 403) and bronchopulmonary dysplasia (see Chapter 416). Pulmonary arterial involvement is sometimes encountered in collagen vascular diseases such as scleroderma (see Chapter 160) and dermatomyositis (see Chapter 159). Functional or structural upper airway obstruction can also produce right ventricular failure. Children with marked obesity are also susceptible to chronic alveolar hypoventilation and right heart failure, termed Pickwickian syndrome. Treatment of the underlying cause is the first priority in patients with secondary pulmonary hypertension (see Chapter 433). Pulmonary hypertension is diagnosed by cardiac catheterization in order to rule out other pulmonary vascular diseases and to test for pulmonary reactivity. A diagnosis of pulmonary hypertension is a mean pulmonary artery pressure of $\geq 25$ mm Hg at rest with a normal pulmonary capillary wedge pressure of $\leq 15$ mm Hg and increased PVR index of $\geq 2$ Wood units/m$^2$. Even though the etiologies are different, most of the drugs used to treat this condition in children are adapted from adult studies. Calcium channel blockers, prostanoids (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan, ambrisentan) and phosphodiesterase 5-inhibitors (sildenafil, tadalafil) are some of the agents used for treatment.

**373.10 Immune Response of the Lung to Injury**

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

Local and systemic diseases can potentially induce an inflammatory response in the lung. Local diseases of the lung capable of inducing the inflammatory response include infectious processes, aspiration, asphyxia, pulmonary congestion, and inhalation of chemical irritants; systemic diseases include sepsis, shock, trauma, and cardiopulmonary bypass. This inflammatory response is mediated through the release of cytokines and other mediators. In the lung, alveolar macrophages are the chief recipients of the early cytokine response, producing tumor necrosis factor-$\alpha$ and interleukin-$\beta$. These cytokines are involved in initiating the inflammatory cascade, resulting in the production of other cytokines, prostaglandins, reactive oxygen species, and upregulating cell adhesion molecules, which, in turn, leads to white cell migration into the lung tissue. The pathophysiologic consequences of the inflammatory response include injury to pulmonary capillary endothelium and the alveolar epithelial cells. Various cytokines and eicosanoids produce pulmonary vasoconstriction, resulting in pulmonary hypertension and increased right ventricular afterload. Injury to the capillary endothelium results in increased permeability and exudation of protein-rich fluid into the pulmonary interstitium and alveoli. Cellular debris and fibrin form the characteristic eosinophilic hyaline membranes along the walls of the alveolar duct. There is sloughing of type 1 pneumocytes. Interstitial and alveolar edema result in decreased FRC, diffusion barrier, intrapulmonary right-to-left shunting across poorly ventilating alveoli, and increase in the $A-aO_2$ gradient. Clinically, $A-aO_2$ gradient $>200$ is characterized as acute lung injury and a gradient $>300$ is termed acute respiratory distress syndrome (ARDS) (see Chapter 71). The inflammatory response to lung injury changes from the fetus to the adult. The fetus and neonate are more likely to have less of an inflammatory cytokine response as demonstrated by a decrease in tumor necrosis factor-$\alpha$ production when mononuclear cells are stimulated when compared to the adult.

The pediatrician must consider the potential adverse effects of therapeutic interventions such as oxygen, endotracheal intubation, and mechanical ventilation as part of the pathophysiologic consequences of ARDS. High concentrations of inspired oxygen have a risk of pulmonary capillary and epithelial cell injury; the concentration of oxygen below which it can be considered safe has not been established. In addition to the potential for nosocomial pneumonia, mechanical ventilation carries the risk of ventilator-induced lung injury from physical stress applied to terminal airways, alveolar epithelium, and pulmonary capillaries. Excessive $V_t$ can itself result in mechanical disruption capable of perpetuating the inflammatory response. If alveoli are allowed to deflate excessively during exhalation, they are subjected to greater stress injury from alveolar recruitment and derecruitment. The mechanical ventilation strategy aimed at minimizing ventilator-induced lung injury in ARDS includes alveolar recruitment and maintenance of adequate PEEP throughout the respiratory cycle with an optimum PEEP, and ventilation with relatively low (6-8 mL/kg) $V_t$.

**373.11 Regulation of Respiration**

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The main function of respiration is to maintain normal blood gas homeostasis to match the metabolic needs of the body with the least amount of energy expenditure. Respiratory rate and $V_t$ are regulated by a complex interaction of controllers, sensors, and effectors. The central respiratory controller consists of a group of neurons in the CNS that receives and integrates the afferent information from sensors and sends motor impulses to effectors to initiate and maintain respiration. Sensors are a variety of receptors located throughout the body. They

Bibliography is available at Expert Consult.
Bibliography


gather chemical and physical information that is sent to the controller either to stimulate or to inhibit its activity. Effectors are the various muscles of respiration that, under the influence of controllers, coordinate respiration and move air in and out of the lung at a given Vt and rate. The respiratory regulatory mechanism itself undergoes a significant maturation process from the neonatal period throughout infancy and early childhood. Sleep states have the potential for profound influences on the control of respiration.

**CENTRAL RESPIRATORY CONTROLLER**

Although the respiratory cycle is often viewed as having an active phase (inspiration) and a passive phase (expiration), rhythmic breathing is a complex process controlled by interaction of numerous distinct groups of neurons. Neuronal control of respiration occurs in 3 phases—inspiration (I), early expiration (E1), and late expiration (E2)—and each may be dysfunctional in disease states. The respiratory controller mechanism comprises 2 functionally and anatomically distinct groups of neurons located in the CNS: 1 for voluntary and the other for automatic control. These areas of respiratory control can function independently but are also capable of interacting with each other.

Voluntary control of respiration resides in the cerebral motor cortex and limbic forebrain structure. Information is received from sensory neurons such as pain, touch, temperature, smell, vision, and emotions, and impulses are sent directly to the respiratory muscles through corticobulbar and corticospinal tracts. Voluntary control of respiration is important for protection from aspiration and inhalation of noxious gases. A certain level of consciousness is necessary to exercise voluntary control of respiration. Patients with CNS injury and toxic or metabolic encephalopathies may lose voluntary control of respirations to varying degrees, depending on the extent of CNS dysfunction.

Automatic control of respiration resides in the brainstem. Central pattern generators (CPGs) are neuronal circuits that generate rhythmic motor output, do not require conscious input, and are responsible for numerous coordinated motor functions such as breathing, swallowing, chewing, walking, and vomiting. The primary CPGs responsible for control of breathing are located in the pons and medulla and include the Bötzinger complex (BotC), pre-Bötzinger complex (pre-BotC), rostral ventral respiratory group and the caudal ventral respiratory group in the medulla, and the Kolliker-Fuse and lateral parabrachial areas in the pons. In addition, an area located adjacent to the facial nerve nucleus, the parafacial respiratory group, is an important modulator of respiration and dysfunction here likely plays a key role in congenital central hypoventilation syndrome (CCHS). Pre-BotC and rostral ventral respiratory group are thought to be the primary sites for inspiratory rhythm generation and BotC and caudal ventral respiratory group are thought to be the primary sites of expiratory rhythm generation under normal circumstances. However, each area is under significant influence from other areas including the nucleus tractus solitarius, which is the area responsible for receiving visceral sensory afferents (see below). The genetic mutation responsible for Prader-Willi syndrome is Hox-regulating genes which is the area responsible for receiving visceral sensor afferents (see above).

CPG areas can also be modulated by neurotransmitters, which can stimulate, inhibit, or modify their activity; they possess receptors for substance P (neurokinin), acetylcholine (nicotinic), glutamate, and opioid μ receptors among others. The embryologic development of these areas is regulated by several genes such as Hox paralogs and Hox-regulating genes *kreisler*/*mauB* and *Krox20*. A group of neurons located in the lower pons is collectively termed the apneustic center, which stimulates pre-BoTC, resulting in prolonged inspiratory gasps (apneusis) interrupted by transient expectancy efforts. Another group of neurons in the upper pons, called the pneumotaxic center, is involved in inhibiting the activity of pre-BoTC. The role of apneustic and pneumotaxic centers is to fine-tune the rhythmic respiratory activity generated by pre-BoTC neurons.

Abnormalities of respiration are commonly encountered in CNS dysfunction and have given clues to the role each of these areas plays in the regulation of respiration. Global CNS depression can manifest as slow and shallow respirations with resultant hypoventilation and respiratory acidosis. Bihemispheric and diencephalic pathologic can lead to Cheyne-Stokes respirations, characterized by periods of apnea interspersed with hyperventilation. Injuries within the rostral brainstem or tegmentum can lead to central neurogenic hyperventilation and respiratory alkalosis. Mid to caudal pontine lesion can result in an apneustic breathing pattern characterized by a prolonged inspiratory pause. Medullary lesions result in ataxic, irregular breathing or apnea.

**SENSORS**

The primary responsibility of the respiratory system is to maintain a steady and adequate supply of oxygen to the blood and help maintain adequate pH by eliminating CO₂. Even short periods of hypoxemia or acidosis are poorly tolerated, and as such, the body has evolved multiple mechanisms to identify hypoxemia and acidosis/increased CO₂. Various receptors throughout the body are responsible for sensing and sending afferent information that modulates the activity of the central respiratory controller. These receptors are sensory nerve endings that respond to changes in their environment. They are termed either chemoreceptors or mechanoreceptors, depending on the type of stimulus that is sensed. Chemoreceptors are classified as central or peripheral, depending on their location.

Central chemoreceptors are so termed because of their location within the CNS. Chemoreceptors sense a change in the chemical composition of body fluid to which they are exposed. Central chemoreceptors reside over a wide area that includes the posterior hypothalamus, cerebellum, locus ceruleus, raphe, and multiple nuclei within the brainstem. Central chemoreceptors bathe in the extracellular fluid of the brain and respond to the changes in the H+ concentration. Information sensing an increase in H+ concentration stimulates ventilatory response of the controller, whereas a decrease inhibits it. The brain’s extracellular fluid, represented by the cerebrospinal fluid (CSF), is separated from the blood by the blood-brain barrier, which is relatively impermeable to H+ and HCO₃⁻ ions but is readily permeable to CO₂.

A rise in Paco₂, is quickly reflected in a similar rise in the CSF. The consequent fall in CSF pH is sensed by the central chemoreceptors, causing stimulation of the controller and increase in ventilation. Changes in Paco₂ result in stimulation or inhibition of ventilation by changes in CSF pH. CSF pH in normal conditions is approximately 7.32. Compared to blood, CSF has much less CO₂ buffering capacity because of a much lower protein concentration. Consequently, the change in CSF pH is more pronounced than that in the blood for the same change in Paco₂. With a persistent elevation in Paco₂, the CSF pH eventually tends to normalize as HCO₃⁻ equilibrates across the blood-brain barrier. Consequently, patients with chronic obstructive pulmonary disease have a relatively normal CSF pH, and they do not show the ventilatory response that is observed with an acute rise in Paco₂. Although O₂ chemosensing has traditionally been described as a function of peripheral chemosensors, multiple brainstem areas, including those with CPG function, are oxygen responsive in the range typical to peripheral chemosensor cells.

Peripheral chemoreceptors are located in carotid bodies just above the bifurcation of the common carotid and external carotid arteries, and in the aortic bodies above and below the aortic arch; the carotid bodies are the most important in humans. The most important variable in determining the activity of the carotid bodies is changes in PaO₂ and much of their afferent output result from changes in membrane potential due to oxygen sensitive potassium channels. Although the carotid bodies have a relatively high metabolic rate, they receive a very high flow for their rather small size. In the setting of normal oxygen delivery, the dissolved oxygen reflected by PaO₂ is sufficient for their metabolism. Stimulation of carotid bodies resulting in increased ventilation occurs when their oxygen supply is decreased below their metabolic requirements. This occurs when there is decreased PaO₂, decreased blood flow (low cardiac output), and impaired oxygen use (cyanide poisoning). Anemia and dyshemoglobinemias do not stimulate carotid body activation unless PaO₂, and the cardiac output are compromised. The relationship of PaO₂ and the stimulation of carotid bodies is nonlinear (Fig. 373-13).
Carotid bodies are activated at a \( \text{PaO}_2 \) of <500 torr and are responsible for roughly a third of the respiratory drive during normal breathing. Their contribution to respiratory drive increases with decreasing age and may be the major determinant to respiratory drive in premature infants. Periodic breathing and other unstable respiratory patterns seen in newborns may be a result of an increased reliance of peripheral oxygen sensing in maintaining respiratory drive. As \( \text{PaO}_2 \) decreases, carotid body afferent output increases. A relatively small increase in ventilation occurs until the \( \text{PaO}_2 \) reaches 100 torr. Where the \( \text{PaO}_2 \) is <100 torr, the carotid body stimulation increases significantly. The carotid body receptor response rate is fast enough to alter their discharge rate during the respiratory cycle as a result of small cyclic changes in \( \text{PaO}_2 \) during inspiration and expiration. At \( \text{PaO}_2 \) levels <50 torr, carotid body stimulation increases exponentially. The most important effect of carotid body stimulation is an increase in respiratory rate and \( \dot{V}_T \). Additional effects include vasoconstriction, bradycardia, systemic hypertension, release of antidiuretic hormone, and stimulation of the adrenal medulla and adrenal cortex. The bradycardia effect of carotid body stimulation is overshadowed by the pulmonary reflex, which is induced by lung inflation and results in tachycardia. Patients in whom lung inflation is prevented are more likely to develop bradycardia after hypoxic stimulation of carotid bodies. Examples of such situations are fetal hypoxia, CNS depression, neuromuscular blockade, myopathy, neuropathy, and controlled ventilation. The peripheral chemoreceptors are responsible for almost all of the increase in ventilation that occurs in response to hypoxemia.

Peripheral chemoreceptors are also stimulated by an increase in \( \text{PaCO}_2 \); this response requires a relatively large change in \( \text{PCO}_2 \) and results in a smaller rise in minute ventilation compared to the effect of \( \text{CO}_2 \) on central chemoreceptors. The peripheral chemoreceptors respond much more quickly (within 1 sec), however, whereas the central chemoreceptors can take minutes to respond. Thus peripheral chemoreceptors are important in the immediate rise in ventilation in response to a large and abrupt increase in \( \text{PaCO}_2 \). Decreased pH also stimulates the peripheral chemoreceptors. The effect of \( \text{pH} \) is regardless of whether the acidosis is a result of respiratory or metabolic causes. Decreased \( \text{PaO}_2 \), increased \( \text{PCO}_2 \), and decreased \( \text{pH} \) act synergistically on carotid bodies. The combined effect is greater than the sum of their individual actions.

In contrast to the central chemoreceptors, the peripheral chemoreceptors are not easily depressed, such as by anesthesia or opiates. They also do not adapt easily to a persistent stimulus such as hypoxia, as do the central chemoreceptors to hypercarbia. The central chemoreceptors in hypoxic patients are relatively unresponsive to \( \text{CO}_2 \) at a time when respirations are predominantly stimulated by effects of hypoxia on peripheral chemoreceptors.

**LUNG RECEPTORS**

**Stretch receptors** are located within the airway smooth muscle. They are stimulated by lung inflation, and the impulse is conducted via the vagus nerve. The main effect of these receptors is to decrease the respiratory rate due to an inhibition of inspiratory muscle activity and an increase in exhalation time. This reflex is termed **Hering-Breuer inflation reflex**. Hering-Breuer deflation reflex stimulates inspiratory muscle activity in response to deflation of the lung. These reflexes are not operative during normal breathing in adults but may be important in newborns. Stretch receptors play an important role in minimizing the energy required for the WOB in respiratory disease. In diseases in which airway resistance is increased (asthma), more energy is needed to overcome airway resistance. Slow and deep breathing is most economical in such a situation because of relatively lower flow rate, and greater alveolar inflation is possible without stretching of the airway smooth muscle earlier during inspiration. In diseases of compliance (pulmonary edema), rapid and shallow breathing is most economical to keep the elastic work at minimum. Because of the stiffer alveoli in such situations, the transpulmonary pressure is transmitted to the airway smooth muscle earlier during inspiration, stimulating the stretch receptors and turning off inspiration.

**Irritant receptors** are present in between the epithelial cells in the airway mucous membrane. They are stimulated by particulate matter, noxious gases, and chemical fumes in the inspired gas, and also by cold air. The vagus nerve is responsible for conducting the impulse. Stimulation of irritant receptors results in bronchoconstriction and hyperpnea.

**J receptors** derive their name because of their juxtacapillary location. They lie in the alveolar walls close to the pulmonary capillaries. Pulmonary capillary engorgement and interstitial and alveolar wall edema provide stimuli for activation of the J receptors, resulting in shallow and rapid respirations and dyspnea. This is seen in left heart failure, ARDS, and interstitial diseases.

**Muscle receptors** important for regulation of respirations are those in the diaphragm and the intercostals. Stretch of the muscle sensed by the muscle spindle is used to control the strength of contraction. Excessive distortion of the diaphragm and the intercostals inhibits inspiratory activity when large negative intrathoracic pressure is required to move air, such as in airway obstruction. The soft chest walls of newborns and young infants are more susceptible to distortion; such children might respond to upper airway obstruction by premature cessation of inspiration and apnea rather than by the prolongation of inspiration required to move sufficient air past the obstruction.

**Arterial baroreceptors** located in aortic arch and carotid sinuses can influence respiration depending on arterial blood pressure. A decrease in blood pressure results in hyperventilation and an increased blood pressure causes hypoventilation.

**Pain and temperature receptors** also influence respirations, and they are especially pronounced in the neonates and young infants. A painful stimulus causes breath holding followed by hyperventilation. Increased skin temperature causes hyperventilation, and hypothermia results in hypoventilation. In the context of cold stimulus, the facial area is most important in causing apnea.

**EFFECTORS**

The most important effectors of respiration are the diaphragm, intercostals, and abdominal muscles. They receive impulses from the controller and effect ventilation. Accessory effectors such as sternocleidomastoids and paraspinal muscles may be called on to make additional contribution to the respiratory efforts in times of need. The effectors can be seriously impaired in malnutrition, spinal injury, and neuromuscular disease.

**SLEEP STATES**

Respiratory regulation is considerably affected by sleep. Sleep, in general, decreases central chemosensitivity to \( \text{CO}_2 \). \( \text{PaCO}_2 \) is increased by a few torr compared to that in the wakeful state. Two broad categories of sleep states exist: **non-rapid eye movement (NREM)** and **REM**
sleep (see Chapter 19). NREM sleep is characterized by high-voltage, slow waves on electroencephalogram and is associated with fragmented mental activity. Muscle tone and movements are relatively unaffected. NREM sleep is likened to a “relatively inactive brain in a movable body.” REM sleep is so termed because of the presence of episodic bursts of REMs.

The most clinically significant aspect of REM sleep is marked suppression of postural muscle tone and lack of spontaneous movements. REM sleep is likened to “a highly activated brain in a paralyzed body.” Descending axons from the dorsal pontine tegmentum region are responsible for the REM sleep-specific characteristic atonia and paralysis. The predominant sleep pattern in premature babies is REM sleep. A full-term newborn has 50% REM sleep. Most of the sleep maturation occurs in the 1st 6 mo of life. Older children and adults spend approximately 20% of their sleep in the REM state. Sleep-related respiratory abnormalities are encountered predominantly in REM sleep.

Depression of muscle tone during REM sleep has 2 major effects. The relaxed and therefore increasingly compliant chest wall retracts inward much more during inspiration than a less-compliant chest wall would, resulting in an impediment to air inflow and a paradoxical (seesaw) pattern of breathing in which the abdomen and the chest wall move asynchronously. The second effect is that of relaxation of the genioglossus, palatal, and other upper airway muscles, causing airway obstruction. REM sleep–related respiratory abnormalities are commonly encountered in premature infants and in children with coexistent anatomic upper airway obstruction, obesity, and neuromuscular dysfunction.

**REGULATION OF RESPIRATION IN SPECIAL SITUATIONS**

**Fetus, Newborns, and Young Infants**

At various stages of development, the response to chemoreceptor and mechanoreceptor stimulation and the efficiency of effectors are markedly different. Unlike adults, who show an immediate and sustained response to hypoxemia characterized by hyperventilation, the newborn exhibits a biphasic response. After an initial brief period (1-2 min) of hyperventilation, the neonate and young infant develop hypoventilation and apnea when hypoxemia is sustained. This explains why such infants are much more prone to develop respiratory arrest in hypoxic states than are older children and adults. Lower gestational age of the infant is associated with a more pronounced and earlier apneic response to hypoxemia. Fetal respiratory activity, for example, is switched off when faced with oxygen deprivation. Maturation of carotid chemoreceptors may be an explanation for the differences in hypoxic response at various stages of development. Sensitivity of CO sensors also undergoes maturation. Compared to adults and older children, neonates and young infants have decreased CO responsiveness, as measured by an increase in minute alveolar ventilation for a given increase in PaCO₂. Theophylline and caffeine increase the central chemoreceptor ventilatory response to CO₂ and decrease the number of apneic spells in premature babies.

The neonatal respiratory muscles are poorly equipped to sustain large workloads; they are more easily fatigued than in older children, and this significantly limits their ability to maintain adequate ventilation in lung disease. Also, the excessive inward retraction of the relatively soft infantile chest wall stimulates the intercostal muscles’ stretch receptors, sending inhibitory impulses to the respiratory center. Young infants are therefore at greater risk of developing apnea when respiratory muscles are subjected to large elastic loads, such as in upper airway obstruction.

Many neurotransmitters involved in regulation of respiration also undergo developmental maturational changes. Serotonergic neurons located in the raphe nuclei possess chemosensitive properties and respond to a decrease in pH. An increase in population of these neurons is associated with increasing chemosensitivity in the developing animal. Abnormalities of the arcuate nucleus, the human equivalent of the rat and cat medullary raphe, have been demonstrated at autopsy on infants dying of sudden infant death syndrome (SIDS; Chapter 375). Cohort studies of Japanese, African-American, and white victims of SIDS have implicated a homozygous gene that encodes for the long allele of the serotonin transporter promoter. SIDS victims are more likely to express the long allele of the serotonin transporter promoter and miss the short allele compared to controls. The delay in development of serotonergic neurons or overexpression of the long allele for serotonin transporter promoter might explain the abnormal respiratory response to adverse conditions, which results in SIDS. Central chemoreception is also severely impaired in congenital central hypoventilation syndrome (CCHS), also known as Ondine’s curse, which results in sleep-associated respiratory arrests. Mutations of PHOX2B gene located on chromosome 4 cause CCHS.

**Chronic Hypoxia and Hypercarbia**

The respiratory control mechanism is altered when exposed to chronic conditions. In patients with chronic pulmonary insufficiency with elevated PaCO₂, the CSF pH has been normalized and the central chemoreceptors become unresponsive to CO₂. Renal compensation results in bicarbonate retention and relative normalization of blood pH. Arterial hypoxemia remains the chief stimulus for ventilation, which is predominantly dependent on peripheral chemoreceptor stimulation by a low PaO₂. Administration of a high amount of oxygen in such patients carries a risk of sudden removal of the hypoxic stimulus, cessation of breathing, exacerbation of hypercarbia and CO₂ narcosis, and coma. Patients with chronic obstructive pulmonary disease and neuromuscular disease are especially susceptible to this complication. Children with bronchopulmonary dysplasia or with muscular dystrophy who have had a high PaCO₂ with or without supplemental oxygen, can develop serious hyperventilation and respiratory acidosis when their PaO₂ is increased more than their baseline with administration of a higher amount of oxygen.

Chronically hypoxic patients, such as those living at high altitude and those with cyanotic heart disease and interstitial lung disease, have a blunted chemoreceptor function and poor response to further hypoxemia. It is of interest to the clinician that children with poorly controlled asthma also show a blunted hypoxic response and can appear to be breathing relatively comfortably in spite of dangerously low PaO₂. Such children and their caretakers are at risk of failing to appreciate the severity of their disease, which can result in delay in instituting appropriate therapy.

*Bibliography is available at Expert Consult.*
Bibliography
A careful history and physical examination are essential to the accurate diagnosis of a child presenting with respiratory signs and/or symptoms. Sometimes, but not always, additional diagnostic tests and modalities are required.

**HISTORY**

The history begins with a narrative provided by the parent/caretaker with input from the patient. The history should include questions about respiratory symptoms (dyspnea, cough, pain, wheezing, snoring, apnea, cyanosis), chronicity, timing during day or night, and associations with activities including exercise or food intake. The respiratory system interacts with a number of other systems, and questions related
to cardiac, gastrointestinal, central nervous, hematologic, and immune systems may be relevant. Questions related to gastrointestinal reflux, congenital abnormalities (airway anomalies, ciliary dyskinesia), or immune status may be important in a patient with repeated pneumonia. The family history is essential and should include inquiries about siblings and other close relatives with similar symptoms or any chronic disease with respiratory components.

**PHYSICAL EXAMINATION**

Respiratory dysfunction usually produces detectable alterations in the pattern of breathing. Values for normal respiratory rates are presented in Table 67-1 (in Chapter 67) and depend on many factors, most importantly, age. Repeated respiratory rate measurements are necessary because respiratory rates, especially in the young, are exquisitely sensitive to extraneous stimuli. Sleeping respiratory rates are more reproducible in infants than those obtained during feeding or activity. These rates vary among infants but average 40–50 breaths/min in the 1st few wk of life and usually <60 breaths/min in the 1st few days of life.

Respiratory control abnormalities can cause the child to breathe at a low rate or periodically. Mechanical abnormalities produce compensatory changes that are generally directed at altering minute ventilation to maintain alveolar ventilation. Decreases in lung compliance require increases in muscular force and breathing rate, leading to variable increases in chest wall retractions and nasal flaring. The respiratory excursions of children with restrictive disease are shallow. An expiratory grunt is common as the child attempts to raise the functional residual capacity (FRC) by closing the glottis at the end of expiration. Children with obstructive disease might take slower, deeper breaths (see Chapter 373). When the obstruction is extrathoracic (from the nose to the mid-trachea), inspiration is more prolonged than expiration, and an inspiratory stridor can usually be heard (see Fig. 373-8 in Chapter 373). When the obstruction is intrathoracic, expiration is more prolonged than inspiration, and the patient often has to make use of accessory expiratory muscles. Intrathoracic obstruction results in air trapping and, therefore, a larger residual volume and, perhaps, greater FRC (see Fig. 373-10 in Chapter 373).

Lung percussion has limited value in small infants because it cannot discriminate between noises originating from tissues that are close to each other. In adolescents and adults, percussion is usually dull in restrictive lung disease, with a pleural effusion, pneumonia, and atelectasis, but it is tympanitic in obstructive disease (asthma, pneumothorax).

Auscultation confirms the presence of inspiratory or expiratory prolongation and provides information about the symmetry and quality of air movement. In addition, it often detects abnormal or adventitious sounds such as stridor (a predominant inspiratory monophonic noise), crackles (or rales) (high-pitched, interrupted sounds found during inspiration and more rarely during early expiration, which denote opening of previously closed air spaces), or wheezes (musical, continuous sounds usually caused by the development of turbulent flow in narrow airways) (Table 374-1). Digital clubbing is a sign of chronic hypoxia and chronic lung disease (Fig. 374-1) but may be a result of nonpulmonary etiologies (Table 374-2).

### Table 374-1 Lung Sound Nomenclature

<table>
<thead>
<tr>
<th>TYPE</th>
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<tbody>
<tr>
<td>DISCONTINUOUS</td>
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<tr>
<td>Fine (high pitch, low amplitude, short duration)</td>
<td>Fine crackles/rales</td>
</tr>
<tr>
<td>Coarse (low pitch, high amplitude, long duration)</td>
<td>Coarse crackles</td>
</tr>
<tr>
<td>CONTINUOUS</td>
<td></td>
</tr>
<tr>
<td>High pitch</td>
<td>Wheezes</td>
</tr>
<tr>
<td>Low pitch</td>
<td>Rhonchi</td>
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### BLOOD GAS ANALYSIS

See also Chapters 373.7 and 373.8.

An arterial blood gas analysis is probably the single most useful rapid test of pulmonary function. Although this analysis does not specify the cause of the condition or the specific nature of the disease process, it can give an overall assessment of the functional state of the respiratory system and clues about the pathogenesis of the disease. Because the detection of cyanosis is influenced by skin color, perfusion, and blood hemoglobin concentration, the clinical detection by inspection is an unreliable sign of hypoxemia. Arterial hypertension, tachycardia, and diaphoresis are late, and not exclusive, signs of hyperventilation.

Blood gas exchange is evaluated most accurately by the direct measurement of arterial pressure of oxygen (PaO2), pressure of carbon dioxide (PaCO2), and pH. The blood specimen is best collected anaerobically in a heparinized syringe containing only enough heparin solution to displace the air from the syringe. The syringe should be sealed, placed in ice, and analyzed immediately. Although these measurements have no substitute in many conditions, they require arterial puncture and have been replaced to a great extent by noninvasive monitoring, such as capillary samples and/or oxygen saturation.

The age and clinical condition of the patient need to be taken into account when interpreting blood gas tensions. With the exception of neonates, values of arterial PaO2 <85 mm Hg are usually abnormal for a child breathing room air at sea level. Calculation of the alveolar–arterial oxygen gradient is useful in the analysis of arterial oxygenation, particularly when the patient is not breathing room air or in the presence of hypercarbia. Values of arterial PaCO2 >45 mm Hg usually indicate hyperventilation or a severe ventilation–perfusion mismatch, unless they reflect respiratory compensation for metabolic alkalosis (see Chapter 55).

**Figure 374-1** Finger clubbing can be measured in different ways. The ratio of the distal phalangeal diameter (DPD) over the interphalangeal diameter (IPD), or the phalangeal depth ratio, is <1 in normal subjects but increases to >1 with finger clubbing. The DPD/IPD can be measured with calipers or, more accurately, with finger casts. The hyponychial angle can be measured from lateral projections of the finger contour on a magnifying screen and is usually <180 degrees in normal subjects but >195 degrees in patients with finger clubbing. For bedside clinical assessment, the Schamroth sign is useful. The dorsal surfaces of the terminal phalanges of similar fingers are placed together. With clubbing, the normal diamond-shaped aperture or “window” at the bases of the nail beds disappears, and a prominent distal angle forms between the ends of the nails. In normal subjects, this angle is minimal or nonexistent. (From Pasterkamp H: The history and physical examination. In Wilmott RW, Boat TF, Bush A, et al, editors: Kendig and Chernick’s disorders of the respiratory tract in children, ed 8, Philadelphia, 2012, Elsevier.)
Nonpulmonary Diseases Associated with Clubbing

<table>
<thead>
<tr>
<th>CARDIAC</th>
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<tbody>
<tr>
<td>Cyanotic congenital heart disease</td>
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<tr>
<td>Subacute bacterial endocarditis</td>
</tr>
<tr>
<td>Chronic congestive heart failure</td>
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</tbody>
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<tr>
<th>HEMATOLOGIC</th>
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<tbody>
<tr>
<td>Thalassemia</td>
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<tr>
<td>Congenital methemoglobinemia (rare)</td>
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</table>

<table>
<thead>
<tr>
<th>GASTROINTESTINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn disease</td>
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<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Chronic dysentery, sprue</td>
</tr>
<tr>
<td>Polyposis coli</td>
</tr>
<tr>
<td>Severe gastrointestinal hemorrhage</td>
</tr>
<tr>
<td>Small bowel lymphoma</td>
</tr>
<tr>
<td>Liver cirrhosis (including α1-antitrypsin deficiency)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid deficiency (thyroid acropathy)</td>
</tr>
<tr>
<td>Chronic pyelonephritis (rare)</td>
</tr>
<tr>
<td>Toxic (e.g., arsenic, mercury, beryllium)</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>Fabry disease</td>
</tr>
<tr>
<td>Raynaud disease, scleroderma</td>
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<tr>
<td>Familial</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>UNILATERAL CLUBBING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders (e.g., subclavian arterial aneurysm, brachial arteriovenous fistula)</td>
</tr>
<tr>
<td>Subluxation of shoulder</td>
</tr>
<tr>
<td>Median nerve injury</td>
</tr>
<tr>
<td>Local trauma</td>
</tr>
</tbody>
</table>

Table 374-2 Nonpulmonary Diseases Associated with Clubbing

<table>
<thead>
<tr>
<th>TRANSLUMINATION OF THE CHEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>In infants up to at least 6 mo of age, a pneumothorax (see Chapter 101.12) can often be diagnosed by transilluminating the chest wall using a fiberoptic light probe. Free air in the pleural space often results in an unusually large halo of light in the skin surrounding the probe. Comparison with the contralateral chest is often very helpful in interpreting findings. This test is unreliable in older patients and in those with subcutaneous emphysema or atelectasis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RADIOGRAPHIC TECHNIQUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-Rays</td>
</tr>
<tr>
<td>A posteroanterior and a lateral view (upright and in full inspiration) should be obtained except in situations in which the child is medically unstable. Portable films, although useful in the latter situation, can give a somewhat distorted image. Expiratory films can be misinterpreted, although a comparison of expiratory and inspiratory films may be useful in evaluating a child with suspected foreign body (localized failure of the lung to empty reflects bronchial obstruction: Chapter 387). If pleural fluid is suspected (see Chapter 410), decubitus films are indicated. Films taken in a recumbent position are difficult to interpret if there is fluid within the pleural space or a cavity.</td>
</tr>
</tbody>
</table>

| Upper Airway Film              |
| A lateral view of the neck can yield invaluable information about upper airway obstruction (see Chapter 385) and particularly about the condition of the retropharyngeal, supraglottic, and subglottic spaces (which should also be viewed in an anteroposterior projection). Knowing the phase of respiration during which the film was taken is often essential for accurate interpretation. Magnified airway films are often helpful in delineating the upper airways. Patients with suggested obstruction should not be unattended in the radiology department. |

| Sinus and Nasal Films         |
| The general utility of roentgenographic examination of the sinuses is uncertain because of the large number of films with positive findings (low sensitivity and specificity). Imaging studies are not necessary to confirm the diagnosis of sinusitis in children younger than age 6 yr. CT scans are indicated if surgery is required, in cases of complications caused by sinus infection, in immunodeficient patients, and for recurrent infections that are not responsive to medical management. |

| Chest Computed Tomography and Magnetic Resonance Imaging |
| Chest CT and MRI can potentially provide images of higher quality and sensitivity than is possible with other imaging modalities. For example, chest CT identifies early abnormalities in young children with cystic fibrosis before pathologic changes are detectable by either plain chest radiographs or pulmonary function testing. Several caveats, however, must be noted. Conventional chest CT involves considerably higher radiation doses than plain films (see Chapter 718). The time required to perform chest CT examinations and the complications of respiratory and body motion mandates the use of sedation for this procedure in many infants and young children. However, improvements in imaging hardware and software have drastically reduced required radiation doses as well as imaging time, obviating the need for sedation in many patients. Chest CT is particularly useful in evaluating very small lesions (e.g., early metastases, mediastinal and pleural lesions, solid or cystic parenchymal lesions, pulmonary embolism, and bronchiectasis). The use of intravenous contrast material during CT imaging enhances vascular structures, distinguishing vessels from other soft-tissue densities. MRI does not involve ionizing radiation, but long imaging times are still involved, and sedation will be necessary to limit spontaneous movement. The utility of MRI of the chest is largely limited to the analysis of mediastinal, hilar, and vascular anatomy. Parenchymal structures and lesions are not well evaluated by MRI. |

| Fluoroscopy                   |
| Fluoroscopy is especially useful for evaluating stridor and abnormal movement of the diaphragm or mediastinum. Many procedures, such as needle aspiration or biopsy of a peripheral lesion, are also best accomplished with the aid of fluoroscopy, CT, or ultrasonography. Videotape recording, which does not increase radiation exposure, can allow detailed study through replay capability during a brief exposure to fluoroscopy. |

| Barium Swallow                |
| A barium swallow study, performed with fluoroscopy and spot films, is indicated in the evaluation of patients with recurrent pneumonia, persistent cough of undetermined cause, stridor, or persistent wheezing. The technique can be modified by using barium of different textures and thicknesses, ranging from thin liquid to solids, to evaluate swallowing mechanics, the presence of vascular rings (see Chapter 386), and tracheoesophageal fistulas (see Chapter 319), especially when aspiration is suspected. A contrast esophagram has been used in evaluating newborns with suggested esophageal atresia, but this procedure entails a high risk of pulmonary aspiration and is not usually recommended. Barium swallows are useful in evaluating suggested gastroesophageal reflux (see Chapter 323), but because of the high incidence of asymptomatic reflux in infants, the applicability of the findings to the clinical problem may be complicated. |

| Pulmonary Arteriography and Aortograms |
| Pulmonary arteriography has been used to allow detailed evaluation of the pulmonary vasculature; has been helpful in assessing pulmonary blood flow and in diagnosing congenital anomalies, such as lobar agenesis, unilateral hyperlucent lung, vascular rings, and arteriovenous malformations; and it is sometimes useful in evaluating solid or cystic
lesions. Thoracic aortograms demonstrate the aortic arch, its major vessels, and the systemic (bronchial) pulmonary circulation. They are useful in evaluating vascular rings and suspected pulmonary sequestration. Although most hemoptyasis is from the bronchial arteries, bronchial arteriography is seldom helpful in diagnosing or treating intrapulmonary bleeding in children. Real-time and Doppler echocardiography and thoracic CT with contrast are noninvasive methods that often reveal similar information and should be considered before arteriography is performed.

Radionuclide Lung Scans
The usual scan uses intravenous injection of material (macroaggregated human serum albumin labeled with 99mTc) that will be trapped in the pulmonary capillary bed. The distribution of radioactivity, proportional to pulmonary capillary blood flow, is useful in evaluating pulmonary embolism and congenital cardiovascular and pulmonary defects. Acute changes in the distribution of pulmonary perfusion can reflect alterations of pulmonary ventilation.

The distribution of pulmonary ventilation can also be determined by scanning after the patient inhales a radioactive gas such as xenon-133. After the intravenous injection of xenon-133 dissolved in saline, pulmonary perfusion and ventilation can be evaluated by continuous recording of the rate of appearance and disappearance of the xenon over the lung. Appearance of xenon early after injection is a measure of perfusion, and the rate of washout during breathing is a measure of ventilation in the pediatric population. The most important indication for this test is to demonstrate defects in the pulmonary arterial distribution that can occur with congenital malformations or pulmonary embolism. Spiral reconstruction CT with contrast medium enhancement is very helpful in evaluating pulmonary thrombi and emboli. Abnormalities in regional ventilation are also easily demonstrable in congenital lobar emphysema, cystic fibrosis, and asthma.

PULMONARY FUNCTION TESTING
See also Chapters 373.7 and 373.9.

The measurement of respiratory function in infants and young children can be difficult because of the lack of cooperation. Attempts have been made to overcome this limitation by creating standard tests that do not require the patient's active participation. Respiratory function tests still provide only a partial insight into the mechanisms of respiratory disease at early ages.

Whether restrictive or obstructive, most forms of respiratory disease cause alterations in lung volume and its subdivisions. Restrictive diseases typically decrease total lung capacity (TLC). TLC includes residual volume, which is not accessible to direct determinations. It must therefore be measured indirectly by gas dilution methods or, preferably, by plethysmography. Restrictive disease also decreases vital capacity (VC). Obstructive diseases produce gas trapping and thus increase residual volume and FRC, particularly when these measurements are considered with respect to TLC.

Airway obstruction is most commonly evaluated from determinations of gas flow in the course of a forced expiratory maneuver. The peak expiratory flow is reduced in advanced obstructive disease. The wide availability of simple devices that perform this measurement at the bedside makes it useful for assessing children who have airway obstruction. Evaluation of peak flows requires a voluntary effort, and peak flows may not be altered when the obstruction is moderate or mild. Other gas flow measurements require that the child inhale to TLC and then exhale as far and as fast as possible for several seconds. Cooperation and good muscle strength are therefore necessary for the measurements to be reproducible. The forced expiratory volume in 1 sec (FEV₁) correlates well with the severity of obstructive diseases.

The maximal midexpiratory flow rate, the average flow during the middle 50% of the forced VC, is a more reliable indicator of mild airway obstruction. Its sensitivity to changes in residual volume and VC, however, limits its use in children with more severe disease. The construction of flow-volume relationships during the forced VC maneuvers overcomes some of these limitations by expressing the expiratory flows as a function of lung volume.

A spirometer is used to measure VC and its subdivisions and expiratory (or inspiratory) flow rates (see Fig. 365-1 in Chapter 365). A simple manometer can measure the maximal inspiratory and expiratory force a subject generates, normally at least 30 cm H₂O, which is useful in evaluating the neuromuscular component of ventilation. Expected normal values for VC, FRC, TLC, and residual volume are obtained from prediction equations based on body height.

Flow rates measured by spirometry usually include the FEV₁ and the maximal midexpiratory flow rate. More information results from a maximal expiratory flow-volume curve, in which expiratory flow rate is plotted against expired lung volume (expressed in terms of either VC or TLC). Flow rates at lung volumes less than approximately 75% VC are relatively independent of effort. Expiratory flow rates at low lung volumes (<50% VC) are influenced much more by small airways than are flow rates at high lung volumes (FEV₁). The flow rate at 25% VC is a useful index of small airway function. Low flow rates at high lung volumes associated with normal flow at low lung volumes suggest upper airway obstruction.

Airway resistance (Rₐw) is measured in a plethysmograph, or, alternatively, the reciprocal of Rₐw airflow conductance, may be used. Because Rₐw measurements vary with the lung volume at which they are taken, it is convenient to use specific airway resistance, SRₐw (SRₐw = Rₐw/lung volume), which is nearly constant in subjects older than 6 yr (normally <7 sec/cm H₂O).

The diffusing capacity for carbon monoxide is related to oxygen diffusion and is measured by rebreathing from a container having a known initial concentration of carbon monoxide or by using a single-breath technique. Decreases in diffusing capacity for carbon monoxide reflect decreases in effective alveolar capillary surface area or decreases in diffusibility of the gas across the alveolar-capillary membrane. Primary diffusion abnormalities are unusual in children; therefore, this test is most commonly employed in children with rheumatologic or autoimmune diseases and in children exposed to toxic drugs to the lungs (e.g., oncology patients) or chest wall radiation. Regional gas exchange can be conveniently estimated with the perfusion-ventilation xenon scan. Determining arterial blood gas levels also discloses the effectiveness of alveolar gas exchange.

Pulmonary function testing, although rarely resulting in a diagnosis, is helpful in defining the type of process (obstruction, restriction) and the degree of functional impairment, in following the course and treatment of disease, and in estimating the prognosis. It is also useful in preoperative evaluation and in confirmation of functional impairment in patients having subjective complaints but a normal physical examination. In most patients with obstructive disease, a repeat test after administering a bronchodilator is warranted.

Most tests require some cooperation and understanding by the patient, and interpretation is greatly facilitated if the test conditions and the patient's behavior during the test are known. Infants and young children who cannot or will not cooperate with test procedures can be studied in a limited number of ways, which often require sedation. Flow rates and pressures during tidal breathing, with or without transient interruption of the flow, may be useful to assess some aspects of Rₐw or obstruction and to measure compliance of the lungs and thorax. Expiratory flow rates can be studied in sedated infants with passive compression of the chest and abdomen with a rapidly inflatable jacket. Gas dilution or plethysmographic methods can also be used in sedated infants to measure FRC and Rₐw.

MICROBIOLOGY: EXAMINATION OF LUNG SECRETIONS
The specific diagnosis of infection in the lower respiratory tract depends on the proper handling of an adequate specimen obtained in an appropriate fashion. Nasopharyngeal or throat cultures are often used but might not correlate with cultures obtained by more-direct techniques from the lower airways. Sputum specimens are preferred and are often obtained from patients who do not expectorate by deep throat swab immediately after coughing or by saline nebulization. Specimens can also be obtained directly from the tracheobronchial tree by nasotracheal aspiration (usually heavily contaminated), by
transtracheal aspiration through the cricothyroid membrane (useful in adults and adolescents but hazardous in children), and in infants and children by a sterile catheter inserted into the trachea either during direct laryngoscopy or through a freshly inserted endotracheal tube. A specimen can also be obtained at bronchoscopy. A percutaneous lung tap or an open biopsy is the only way to obtain a specimen absolutely free of oral flora.

A specimen obtained by direct expectoration is usually assumed to be of tracheobronchial origin, but often, especially in children, it is not from this source. The presence of macrophages (large mononuclear cells) is the hallmark of tracheobronchial secretions. Nasopharyngeal and tracheobronchial secretions can contain ciliated epithelial cells, which are more commonly found in sputum. Nasopharyngeal and oral secretions often contain large numbers of squamous epithelial cells. Sputum can contain both ciliated and squamous epithelial cells.

During sleep, mucociliary transport continually brings tracheobronchial secretions to the pharynx, where they are swallowed. An early-morning fasting gastric aspirate often contains material from the tracheobronchial tract that is suitable for culture for acid-fast bacilli.

The absence of polymorphonuclear leukocytes in a Wright-stained smear of sputum or bronchoalveolar lavage (BAL) fluid containing adequate numbers of macrophages may be significant evidence against a bacterial infectious process in the lower respiratory tract, assuming that the patient has normal neutrophil counts and function. Eosinophils suggest allergic disease. Iron stains can reveal hemosiderin granules within macrophages, suggesting pulmonary hemosiderosis. Specimens should also be examined by Gram stain. Bacteria within or near macrophages and neutrophils can be significant. Viral pneumonia may be accompanied by intranuclear or cytoplasmic inclusion bodies visible on Wright-stained smears, and fungal forms may be identifiable on Gram or silver stains.

With advances in the area of genomics and the speed with which it is possible to identify microbes, microbiologic analysis has been expanded. For example, specific bacteria in the lungs of children with cystic fibrosis (see Chapter 403) are linked to morbidity and mortality. There is a correlation between patient age and morbidity and mortality (as expected) but that there are important microbes that are correlated either negatively or positively with early or late pathogenic processes. Pseudomonas aeruginosa and Stenotrophomonas maltophilia (see Chapter 205) have a strong positive correlation with patient age in cystic fibrosis. The microbiota diversity is much broader in those who are healthier individuals or those that are younger patients with cystic fibrosis than the older and sicker population.

In addition, the microbiomes (see Chapter 171) in the respiratory tract of smokers and nonsmokers differ substantially. In all patients, most of the bacteria found in the lungs are also present in the oral cavity, as expected, although some bacteria, such as Haemophilus and enterobacteria are much more represented in the lungs than in the mouth. Principal differences between smokers and nonsmokers are found in the microbiome in the mouth, for example, bacteria like Neisseria.

**EXERCISE TESTING**

Exercise testing (see Chapter 423.5) is a more-direct approach for detecting diffusion impairment as well as other forms of respiratory disease. Exercise is a strong provocateur of bronchospasm in susceptible patients, so exercise testing can be useful in the diagnosis of patients with asthma that is only apparent with activity. Measurements of heart and respiratory rate, minute ventilation, oxygen consumption, carbon dioxide production, and arterial blood gases during incremental exercise loads often provide invaluable information about the functional nature of the disease. Often a simple assessment of the patient’s exercise tolerance in conjunction with other, more static forms of respiratory function testing can allow a distinction between respiratory and nonrespiratory disease in children.

**SLEEP STUDIES**

See Chapter 19.

**AIRWAY VISUALIZATION AND LUNG SPECIMEN-BASED DIAGNOSTIC TESTS**

**Laryngoscopy**

The evaluation of stridor, problems with vocalization, and other upper airway abnormalities usually requires direct inspection. Although indirect (mirror) laryngoscopy may be reasonable in older children and adults, it is rarely feasible in infants and small children. Direct laryngoscopy may be performed with either a rigid or a flexible instrument. The safe use of the rigid scope for examining the upper airway requires topical anesthesia and either sedation or general anesthesia, whereas the flexible laryngoscope can often be used in the office setting with or without sedation. Further advantages to the flexible scope include the ability to assess the airway without the distortion that may be introduced by the use of the rigid scope and the ability to assess airway dynamics more accurately. Because there is a relatively high incidence of concomitant lesions in the upper and lower airways, it is often prudent to examine the airways above and below the glottis, even when the primary indication is in the upper airway (stridor).

**Bronchoscopy and Bronchoalveolar Lavage**

Bronchoscopy is the inspection of the airways. BAL is a method used to obtain a representative specimen of fluid and secretions from the lower respiratory tract, which is useful for the cytologic and microbiologic diagnosis of lung diseases, especially in those who are unable to expectorate sputum. BAL is performed after the general inspection of the airways and before tissue sampling with a brush or biopsy forceps. BAL is accomplished by gently wedging the scope into a lobar, segmental, or subsegmental bronchus and sequentially instilling and withdrawing sterile nonbacteriostatic saline in a volume sufficient to ensure that some of the aspirated fluid contains material that originated from the alveolar space. Nonbronchoscopic BAL can be performed, although with less accuracy and, therefore, less-reliable results, in intubated patients by instilling and withdrawing saline through a catheter passed through the artificial airway and blindly wedged into a distal airway. In either case, the presence of alveolar macrophages documents that an alveolar sample has been obtained. Because the methods used to perform BAL involve passage of the equipment through the upper airway, there is a risk of contamination of the specimen by upper airway secretions. Careful cytologic examination and quantitative microbiologic cultures are important for correct interpretation of the data. BAL can often obviate the need for more-invasive procedures such as open lung biopsy, especially in immunocompromised patients.

Indications for diagnostic bronchoscopy and BAL include recurrent or persistent pneumonia or atelectasis, unexplained or localized and persistent wheeze, the suspected presence of a foreign body, hemoptysis, suspected congenital anomalies, mass lesions, interstitial disease, and pneumonia in the immunocompromised host. Indications for therapeutic bronchoscopy and BAL include bronchial obstruction by mass lesions, foreign bodies or mucus plugs, and general bronchial toilet and bronchopulmonary lavage. The patient undergoing bronchoscopy ventilates around the flexible scope, whereas with the rigid scope, ventilation is accomplished through the scope. Rigid bronchoscopy is preferentially indicated for extracting foreign bodies, for removing tissue masses, and in patients with massive hemoptysis. In other cases, the flexible scope offers the advantages that it can be passed through endotracheal or tracheostomy tubes, can be introduced into bronchi that come off the airway at acute angles, and can be safely and effectively inserted with topical anesthesia and conscious sedation.

Regardless of the instrument used, the procedure performed, or its indications, the most common complications are related to sedation. The relatively more common complications related to the bronchoscopy itself include transient hypoxemia, laryngospasm, bronchospasm, and cardiac arrhythmias. Iatrogenic infection, bleeding, pneumothorax, and pneumomediastinum are rare but reported complications of bronchoscopy or BAL. Bronchoscopy in the setting of possible pulmonary abscess or hemoptysis must be undertaken with advance preparations for definitive airway control, mindful of the possibility that pus or blood might flood the airway. Subglottic edema is a more common complication of rigid bronchoscopy than of flexible procedures, in
which the scopes are smaller and less likely to traumatize the mucosa. Postbronchoscopy croup is treated with oxygen, mist, vasoconstrictor aerosols, and corticosteroids as necessary.

**Thoracoscopy**
The pleural cavity can be examined through a thoracoscope, which is similar to a rigid bronchoscope. The thoracoscope is inserted through an intercostal space and the lung is partially deflated, thus allowing the operator to view the surface of the lung, the pleural surface of the mediastinum and diaphragm, and the parietal pleura. Multiple thoracoscopic instruments can be inserted, allowing endoscopic biopsy of the lung or pleura, resection of blebs, abrasion of the pleura, and ligation of vascular rings.

**Thoracentesis**
For diagnostic or therapeutic purposes, fluid can be removed from the pleural space by needle. Generally, as much fluid as possible should be withdrawn, and an upright chest roentgenogram should be obtained after the procedure. Complications of thoracentesis include infection, pneumothorax, and bleeding. Thoracentesis on the right may be complicated by puncture or laceration of the capsule of the liver and, on the left, by puncture or laceration of the capsule of the spleen. Specimens obtained should always be cultured, examined microscopically for evidence of bacterial infection, and evaluated for total protein and total differential cell counts. Lactic acid dehydrogenase, glucose, cholesterol, triglyceride (chylous), and amylase determinations may also be useful. If malignancy is suspected, cytologic examination is imperative.

Transudates result from mechanical factors influencing the rate of formation or reabsorption of pleural fluid and generally require no further diagnostic evaluation. Exudates result from inflammation or other disease of the pleural surface and underlying lung and require a more complete diagnostic evaluation. In general, transudates have a total protein of <3 g/dL or a ratio of pleural protein to serum protein <0.5, a total leukocyte count of fewer than 2,000/mm³ with a predominance of mononuclear cells, and low lactic dehydrogenase levels. Exudates have high protein levels and a predominance of polymorphonuclear cells (although malignant or tuberculous effusions can have a higher percentage of mononuclear cells). Complicated exudates often require continuous chest tube drainage and have a pH <7.2. Tuberculous effusions can have low glucose and high cholesterol content.

**Lung Tap**
Using a technique similar to that used for thoracentesis, a percutaneous lung tap is the most direct method of obtaining bacteriologic specimens from the pulmonary parenchyma and is the only technique other than open lung biopsy not associated with at least some risk of contamination by oral flora. After local anesthesia, a needle attached to a syringe containing nonbacteriostatic sterile saline is inserted using aseptic technique through the inferior aspect of an intercostal space in the area of interest. The needle is rapidly advanced into the lung; the saline is injected and reaspirated, and the needle is withdrawn. These actions are performed as quickly as possible. This procedure usually yields a few drops of fluid from the lung, which should be cultured and examined microscopically.

Major indications for a lung tap are infiltrates of undetermined cause, especially those unresponsive to therapy in immunosuppressed patients who are susceptible to unusual organisms. Complications are the same as for thoracentesis, but the incidence of pneumothorax is higher and somewhat dependent on the nature of the underlying disease process. In patients with poor pulmonary compliance, such as children with *Pneumocystis* pneumonia, the rate can approach 30%, with 5% requiring chest tubes. Bronchopulmonary lavage has replaced lung taps for most purposes.

**Lung Biopsy**
Lung biopsy may be the only way to establish a diagnosis, especially in protracted, noninfectious disease. In infants and small children, thoracoscopic or open surgical biopsies are the procedures of choice, and...
Chapter 374  •  Diagnostic Approach to Respiratory Disease  1998.e1

Bibliography


Sudden infant death syndrome (SIDS) is defined as the sudden, unexpected death of an infant that is unexplained by a thorough post-mortem examination, which includes a complete autopsy, investigation of the scene of death, and review of the medical history. An autopsy is essential to identify possible natural explanations for sudden unexpected death such as congenital anomalies or infection and to diagnose traumatic child abuse (Tables 375-1, 375-2, and 375-3; see Chapter 40). The autopsy typically cannot distinguish between SIDS and intentional suffocation, but the scene investigation and medical history may be of help if inconsistencies are evident. Sudden unexpected infant death (SUID) is a term that encompasses all sudden unexpected infant deaths. Unexplained SUID is equivalent to SIDS.

EPIDEMIOLOGY
SIDS is the third leading cause of infant mortality in the United States, accounting for approximately 8% of all infant deaths. It is the most common cause of postneonatal infant mortality, accounting for 40-50% of all deaths between 1 mo and 1 yr of age. The annual rate of SIDS in the United States was stable at 1.3-1.4 per 1,000 live births (approximately 7,000 infants/year) before 1992, when it was recommended that infants sleep nonprone as a way to reduce risk for SIDS. Since then, particularly after initiation of the national Back to Sleep campaign in 1994, the rate of SIDS progressively declined and then leveled off in 2001 at 0.55 per 1,000 live births (2,234 infants). The rates have remained stagnant since that time; in 2009 it was 0.54 per 1,000 live births (2,231 infants). The decline in the number of SIDS deaths in the United States and other countries has been attributed to increasing use of the supine position for sleep. In 1992, 82% of sampled infants in the United States were placed prone for sleep. Several other countries have decreased prone sleeping prevalence to 52%, but in the United States in 2009, 11% of infants were still being placed prone for sleep and 13% were being placed in the side position. Among black infants, these rates were even higher: 22% prone and 22% side in 2009.
**Table 375-1** Differential Diagnosis of Sudden Unexpected Infant Death

<table>
<thead>
<tr>
<th>CAUSE OF DEATH</th>
<th>PRIMARY DIAGNOSTIC CRITERIA</th>
<th>CONFOUNDING FACTOR(S)</th>
<th>FREQUENCY DISTRIBUTION (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPLAINED AT AUTOPSY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural</td>
<td>History, autopsy, and cultures</td>
<td>If minimal findings: SIDS</td>
<td>18-20*</td>
</tr>
<tr>
<td>Infections</td>
<td>History and autopsy</td>
<td>If minimal findings: SIDS</td>
<td>35-46†</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>History, scene investigation, autopsy</td>
<td>Traumatic child abuse</td>
<td>14-24†</td>
</tr>
<tr>
<td>Unintentional injury</td>
<td>Autopsy and scene investigation</td>
<td>Unintentional injury</td>
<td>13-24*</td>
</tr>
<tr>
<td>Traumatic child abuse</td>
<td>History and autopsy</td>
<td>If minimal findings: SIDS, or intentional suffocation</td>
<td>12-17*</td>
</tr>
<tr>
<td>Other natural causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNEXPLAINED AT AUTOPSY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIDS</td>
<td>History, scene investigation, absence of explainable cause at autopsy</td>
<td>Intentional suffocation</td>
<td>80-82%</td>
</tr>
<tr>
<td>Intentional suffocation (filicide)</td>
<td>Perpetrator confession, absence of explainable cause at autopsy</td>
<td>SIDS</td>
<td>Unknown, but &lt;5% of all SUID</td>
</tr>
<tr>
<td>Accidental suffocation or strangulation in bed (ASSB)</td>
<td>History and scene investigation, ideally including doll re-enactment</td>
<td>Assigned to ICD-10 code (SIDS) for U.S. vital statistics database</td>
<td>Varies with individual medical examiners and coroners</td>
</tr>
</tbody>
</table>

*As a percentage of all sudden unexpected infant deaths explained at autopsy.
†As a percentage of all natural causes of sudden unexpected infant deaths explained at autopsy.
ICD-10, International Classification of Diseases, Version 10; SIDS, sudden infant death syndrome; SUDI, sudden unexpected death in infancy.

**Table 375-2** Conditions That Can Cause Apparent Life-Threatening Events or Sudden Unexpected Infant Death

<table>
<thead>
<tr>
<th>CENTRAL NERVOUS SYSTEM</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Arteriovenous malformation</td>
<td></td>
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<tr>
<td>Subdural hematoma</td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Congenital central hypoventilation</td>
<td></td>
<td></td>
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<tr>
<td>Neuromuscular disorders (Werdnig-Hoffmann disease)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chiari crisis</td>
<td></td>
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<tr>
<td>Leigh syndrome</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CARDIAC</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subendocardial fibroelastosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td></td>
<td></td>
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<tr>
<td>Anomalous coronary artery</td>
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<tr>
<td>Myocarditis</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Arrhythmias (prolonged Q-T syndrome, Wolff-Parkinson-White syndrome, congenital heart block)</td>
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<tr>
<td>PULMONARY</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary hypertension</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vocal cord paralysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngotracheal disease</td>
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<td></td>
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<tr>
<td>GASTROINTESTINAL</td>
<td></td>
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<tr>
<td>Diarrhea and/or dehydration</td>
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<td></td>
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<tr>
<td>Gastroesophageal reflux</td>
<td></td>
<td></td>
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<tr>
<td>Volvulus</td>
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<tr>
<td>ENDOCRINE–METABOLIC</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Congenital adrenal hyperplasia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Malignant hyperpyrexia</td>
<td></td>
<td></td>
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<tr>
<td>Long- or medium-chain acyl coenzyme A deficiency</td>
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<tr>
<td>Hyperammonemias (urea cycle enzyme deficiencies)</td>
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<tr>
<td>Glutanic aciduria</td>
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<tr>
<td>Carnitine deficiency (systemic or secondary)</td>
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<tr>
<td>Glycogen storage disease type I</td>
<td></td>
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<tr>
<td>Maple syrup urine disease</td>
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<td></td>
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<tr>
<td>Congenital lactic acidosis</td>
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<tr>
<td>Biotinidase deficiency</td>
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<tr>
<td>INFECTION</td>
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<td></td>
<td></td>
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<tr>
<td>Sepsis</td>
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<td></td>
<td></td>
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<tr>
<td>Meningitis</td>
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<td></td>
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<tr>
<td>Encephalitis</td>
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<td></td>
<td></td>
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<tr>
<td>Brain abscess</td>
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<td></td>
<td></td>
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<tr>
<td>Pyelonephritis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bronchiolitis (respiratory syncytial virus)</td>
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<tr>
<td>Infant botulism</td>
<td></td>
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<tr>
<td>Pertussis</td>
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<tr>
<td>TRAUMA</td>
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<td></td>
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</tr>
<tr>
<td>Child abuse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental or intentional suffocation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical trauma</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Factitious syndrome (formerly Munchausen syndrome) by proxy</td>
<td></td>
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<tr>
<td>POISONING (INTENTIONAL OR UNINTENTIONAL)</td>
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<tr>
<td>Boric acid</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Carbon monoxide</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Salicylates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
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<td></td>
<td></td>
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<tr>
<td>Ipecac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
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</tr>
</tbody>
</table>

There is increasing evidence that infant deaths previously classified as SIDS are now being classified by medical examiners and coroners as from other causes, notably accidental suffocation and strangulation in bed. Between 1994 and 2004, there has been a quadrupling in the rates of accidental suffocation and strangulation in bed, from 2.8-12.5 deaths per 100,000 live births. These sudden and unexpected infant deaths are primarily associated with an unsafe sleeping environment such as prone position or in bed with parents. Based on these trends and the commonality of many of the sleep environment risk factors that are associated with both SIDS and other sleep-related SUID, risk reduction measures will be later described that are applicable to all sleep-related SUID.

**PATHOLOGY**

There are no autopsy findings pathognomonic for SIDS and no findings required for the diagnosis. There are some common findings. Petechial hemorrhages are found in 68-95% of cases and are more extensive than in explained causes of infant mortality. Pulmonary edema is often present and may be substantial. The reasons for these findings are unknown.

SIDS infants have several identifiable changes in the lungs and other organs and in brainstem structure and function. Nearly 65% of SIDS infants have structural disorders of preexisting, chronic, low-grade asphyxia, and other studies have identified biochemical markers of asphyxia. SIDS victims have higher levels of vascular endothelial growth factor (VEGF) in the cerebrospinal fluid. These increases may be related to VEGF polymorphisms (see “Genetic Risk Factors” below and Table 375-4) or might indicate recent hypoxic events, because VEGF is upregulated by hypoxia. Brainstem findings include a persistent increase of dendritic spines and delayed maturation of synapses in the medullary respiratory centers, and decreased tyrosine hydroxylase immunoreactivity and catecholaminergic neurons. Cardiac muscle munc18-1 receptor overexpression has also been reported in SIDS infants compared to infants who died from noncardiac causes. The regulatory mechanism may be related to increased acetylcholine esterase enzyme activity. The retrotrapezoid nucleus is one of the primary sites of central chemoreception and respiratory drive, and structural and/or PHOX2B-expression abnormalities have been reported in significantly more SIDS and other SUID cases than controls.

**Table 375-3**

<table>
<thead>
<tr>
<th>Differential Diagnosis of Recurrent Sudden Infant Death in a Sibship</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDIOPATHIC</td>
</tr>
<tr>
<td>Recurrent sudden infant death syndrome</td>
</tr>
<tr>
<td>CENTRAL NERVOUS SYSTEM</td>
</tr>
<tr>
<td>Congenital central hypoventilation</td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
</tr>
<tr>
<td>Leigh syndrome</td>
</tr>
<tr>
<td>CARDIAC</td>
</tr>
<tr>
<td>Endocardial fibroelastosis</td>
</tr>
<tr>
<td>Wolff-Parkinson-White syndrome</td>
</tr>
<tr>
<td>Prolonged Q-T syndrome or other cardiac channelopathy</td>
</tr>
<tr>
<td>Congenital heart block</td>
</tr>
<tr>
<td>PULMONARY</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>ENDOCRINE–METABOLIC</td>
</tr>
<tr>
<td>See Table 375-2</td>
</tr>
<tr>
<td>INFECTION</td>
</tr>
<tr>
<td>Disorders of immune host defense</td>
</tr>
<tr>
<td>CHILD ABUSE</td>
</tr>
<tr>
<td>Fictitious or infanticide</td>
</tr>
<tr>
<td>Factitious syndrome (formerly Munchausen syndrome) by proxy</td>
</tr>
</tbody>
</table>


**Table 375-4**

<table>
<thead>
<tr>
<th>Identified Genes for Which the Distribution of Polymorphisms Differs in Sudden Infant Death Syndrome Infants Compared to Control Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIAC CHANNELopathies (11)</td>
</tr>
<tr>
<td>Potassium ion channel genes ( KCNE2, KCNH2, KCNQ1, KCNJ8)</td>
</tr>
<tr>
<td>Sodium ion channel gene (SCN5A) (long QT syndrome 3, Brugada syndrome)</td>
</tr>
<tr>
<td>GPD1-L-encoded connexin43 (Brugada syndrome)</td>
</tr>
<tr>
<td>SCN3B (Brugada syndrome)</td>
</tr>
<tr>
<td>CAV3 (long QT syndrome 9)</td>
</tr>
<tr>
<td>SCN4B (long QT syndrome 10)</td>
</tr>
<tr>
<td>SNTA-1 (long QT syndrome 11)</td>
</tr>
<tr>
<td>RyR2 (catecholaminergic polymorphic ventricular tachycardia)</td>
</tr>
<tr>
<td>SEROTONIN (5-HT) (3)</td>
</tr>
<tr>
<td>5-HT transporter protein (5-HTT)</td>
</tr>
<tr>
<td>Intron 2 of SLC6A4 (variable number tandem repeat [VNTR] polymorphism)</td>
</tr>
<tr>
<td>5-HT fifth Ewing variant (FEV) gene</td>
</tr>
<tr>
<td>GENES PERTINENT TO DEVELOPMENT OF AUTONOMIC NERVOUS SYSTEM (9)</td>
</tr>
<tr>
<td>Paired-like homeobox 2a (PHOX2A)</td>
</tr>
<tr>
<td>PHOX2B</td>
</tr>
<tr>
<td>Rearranged during transfection factor (RET)</td>
</tr>
<tr>
<td>Endothelin converting enzyme-1 (ECE1)</td>
</tr>
<tr>
<td>T-cell leukemia homeobox (TLX3)</td>
</tr>
<tr>
<td>Engrailed-1 (EN1)</td>
</tr>
<tr>
<td>Tyrosine hydroxylase (THO1)</td>
</tr>
<tr>
<td>Monamine oxidase A (MAOA)</td>
</tr>
<tr>
<td>Sodium/proton exchanger 3 (NHE3) (medullary respiratory control)</td>
</tr>
<tr>
<td>INFECTION AND INFLAMMATION (8)</td>
</tr>
<tr>
<td>Complement C4A</td>
</tr>
<tr>
<td>Complement C4B</td>
</tr>
<tr>
<td>Interleukin-1RN (gene encoding IL-1 receptor antagonist [ra]; proinflammatory)</td>
</tr>
<tr>
<td>Interleukin-6 (IL-6; proinflammatory)</td>
</tr>
<tr>
<td>Interleukin-8 (IL-8; proinflammatory; associated with prone sleeping position)</td>
</tr>
<tr>
<td>Interleukin-10 (IL-10)</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF) (proinflammatory)</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF-α) (proinflammatory)</td>
</tr>
<tr>
<td>OTHER (3)</td>
</tr>
<tr>
<td>Mitochondrial DNA (mtDNA) polymorphisms (energy production)</td>
</tr>
<tr>
<td>Flavin-monooxygenase 3 (FM03) (enzyme metabolizes nicotine; risk factor with smoking mothers)</td>
</tr>
<tr>
<td>Aquaporin-4 (T allele and CT/TT genotype associated with maternal smoking and with increased brain/body weight ratio in SIDS infants)</td>
</tr>
</tbody>
</table>


The ventral medulla has been a particular focus for studies in SIDS infants. It is an integrative area for vital autonomic functions including breathing, arousal, and chemo sensory function. Quantitative 3-dimensional anatomic studies indicate that some SIDS infants have hypoplasia of the arcuate nucleus and up to 60% have histopathologic evidence of less-extensive bilateral or unilateral hypoplasia. Consistent with the apparent overlap between putative mechanisms for SIDS and for unexpected late fetal deaths, approximately 30% of late unexpected and unexplained stillbirths also have hypoplasia of the arcuate nucleus.

Neurotransmitter studies of the arcuate nucleus have also identified receptor abnormalities in some SIDS infants that involve several receptor types relevant to state-dependent autonomic control overall and to ventilatory and arousal responsiveness in particular. These deficits
include significant decreases in binding to kainate, muscarinic cholinergic, and serotonin (5-HT) receptors. Studies of the ventral medulla have identified morphologic and biochemical deficits in 5-HT neurons and decreased γ-aminobutyric acid receptor A receptor binding in the medullary serotonergic system. Immunohistochemical analyses reveal an increased number of 5-HT neurons and an increase in the fraction of 5-HT neurons showing an immature morphology, suggesting a failure or delay in the maturation of these neurons. High neuronal levels of interleukin-1β are present in the arcuate and dorsal vagal nuclei in SIDS victims compared to controls, perhaps contributing to molecular interactions affecting cardiorespiratory and arousal responses.

The neuropathologic data provide compelling evidence for altered 5-HT homeostasis, creating an underlying vulnerability contributing to SIDS. 5-HT is an important neurotransmitter and the 5-HT neurons in the medulla project extensively to neurons in the brainstem and spinal cord that influence respiratory drive and arousal, cardiovascular control including blood pressure, circadian regulation and non–rapid eye movement (REM) sleep, thermoregulation, and upper airway reflexes. Medullary 5-HT neurons may be respiratory chemosensors and may be involved with respiratory responses to intermittent hypoxia and respiratory rhythm generation. Decreases in 5-HT₁A and 5-HT₁D receptor immunoreactivity have been observed in the dorsal nucleus of the vagus, solitary nucleus, and ventrolateral medulla. There are extensive serotoninergic brainstem abnormalities in SIDS infants, including increased 5-HT neuronal count, a lower density of 5-HT₁A receptor-binding sites in regions of the medulla involved in homeostatic function, and a lower ratio of 5-HT transporter (5-HTT) binding density to 5-HT neuronal count in the medulla. Male SIDS infants have lower receptor-binding density than female SIDS infants. These findings suggest that the synthesis and availability of 5-HT is decreased within 5-HT pathways and hence impairs neuronal firing. Medullary tissue levels of 5-HT and its primary biosynthetic enzyme (tryptophan hydroxylase) were observed to be lower in SIDS cases compared to age-matched controls, indicating reduced 5-HT synthesis and hence a deficiency in 5-HT.

**ENVIRONMENTAL RISK FACTORS**

Declines of 50% or more in rates of SIDS in the United States and around the world have occurred following national education campaigns directed at reducing risk factors associated with SIDS. The reductions in risk appear to be related primarily to decreases in placing infants prone for sleep and increases in placing them supine. A number of other risk factors also have significant associations with SIDS (Table 375-5). Although many are nonmodifiable and most of the modifiable factors have not changed appreciably, self-reported maternal smoking prevalence during pregnancy has decreased by 25% in the past decade in the United States.

**Nonmodifiable Environmental Risk Factors**

Lower socioeconomic status has consistently been associated with higher risk, although SIDS affects infants from all social strata. In the United States, African-American, Native American, and Alaskan Native infants are 2-3 times more likely than white infants to die of SIDS, whereas Asian, Pacific Islander, and Hispanic infants have the lowest incidence. Some of this disparity may be related to the higher concentration of poverty and other adverse environmental factors found within some, but not all, of the communities with higher incidence.

Infants are at greatest risk of SIDS at 2-4 mo of age, with most deaths having occurred by 6 mo. This characteristic age has decreased in some countries as the SIDS incidence has declined, with deaths occurring at earlier ages and with a flattening of the peak age incidence. Similarly, the commonly observed winter seasonal predominance of SIDS has declined or disappeared in some countries as prone prevalence has decreased, supporting prior findings of an interaction between sleep position and factors more common in colder months (overheating as a consequence of elevated interior temperatures or bundling with blankets and heavy clothing, or infection). Male infants are 30-50% more likely to be affected than female infants.

### Table 375-5 Environmental Factors Associated with Increased Risk for Sudden Infant Death Syndrome

<table>
<thead>
<tr>
<th>MATERNAL AND ANTENATAL RISK FACTORS</th>
<th>ENVIRONMENTAL FACTORS ASSOCIATED WITH INCREASED RISK FOR SUDDEN INFANT DEATH SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Elevated 2nd trimester serum α-fetoprotein</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Smoking</td>
</tr>
<tr>
<td>Drug use (cocaine, heroin)</td>
<td>Alcohol use</td>
</tr>
<tr>
<td>Nutritional deficiency</td>
<td>Drug use (cocaine, heroin)</td>
</tr>
<tr>
<td>Inadequate prenatal care</td>
<td>Nutritional deficiency</td>
</tr>
<tr>
<td>Younger age</td>
<td>Race and ethnicity (African-American and Native American, other minorities)</td>
</tr>
<tr>
<td>Lower education</td>
<td>Growth failure</td>
</tr>
<tr>
<td>Single marital status</td>
<td>No breast-feeding</td>
</tr>
<tr>
<td>Shorter interpregnancy interval</td>
<td>No pacifier (dummy)</td>
</tr>
<tr>
<td>Intrauterine hypoxia</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>Prone and side sleep position</td>
</tr>
<tr>
<td></td>
<td>Recent febrile illness (mild infections)</td>
</tr>
<tr>
<td></td>
<td>Inadequate immunizations</td>
</tr>
<tr>
<td>Smoking exposure (prenatal and postnatal)</td>
<td>Smoking exposure (prenatal and postnatal)</td>
</tr>
<tr>
<td>Soft sleeping surface, soft bedding</td>
<td>Smoking exposure (prenatal and postnatal)</td>
</tr>
<tr>
<td>Bed sharing with parent(s) or other children</td>
<td>Smoking exposure (prenatal and postnatal)</td>
</tr>
<tr>
<td>Thermal stress, overheating</td>
<td>Colder season, no central heating</td>
</tr>
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</tbody>
</table>
Drug and Alcohol Use

Most studies link maternal prenatal drug use, especially opiates, with an increased risk of SIDS, ranging from a 2-15-fold increased risk. Most but not all studies have not found an association between maternal alcohol use prenatally or postnatally and SIDS. In one study of Northern Plains Indians, periconceptional alcohol use and binge drinking in the 1st trimester were associated with a 6-fold and an 8-fold increased risk of SIDS, respectively. A Danish cohort study found that mothers admitted to the hospital for an alcohol- or drug-related disorder at any time before or after the birth of their infants had a 3-times higher risk of their infant dying from SIDS, and a Dutch study reported that maternal alcohol consumption in the 24 hr before the infant died carried a 2-8-fold increased risk of SIDS. Siblings of infants with fetal alcohol syndrome have a 10-fold increased risk of SIDS compared to controls.

Infant Sleep Environment

Sleeping prone has consistently been shown to increase the risk of SIDS. As rates of prone positioning have decreased in the general population, the odds ratios for SIDS in infants still sleeping prone have increased. The highest risk of SIDS occurs in infants who are usually placed nonprone, but placed prone for last sleep (“unaccustomed prone”) or found prone (“secondary prone”). The “unaccustomed prone” position may be more likely to occur in daycare or other settings outside the home and highlights the need for all infant caretakers to be educated about appropriate sleep positioning.

Side-sleeping is also a significant risk factor. The initial SIDS risk-reduction campaign recommendations considered side sleeping to be nearly equivalent to the supine position in reducing the risk of SIDS. Subsequent studies documented that side-sleeping infants were twice as likely to die of SIDS as infants sleeping supine. This increased risk might relate to the relative instability of the position, with some infants placed on the side rolling to the prone position. With the overall decrease in rates of placing infants prone for sleep, a higher proportion of SIDS is now attributed to being placed on the side for sleeping than for being placed prone. Nevertheless, the majority of SIDS occurrences are associated with being found prone. The current recommendations call for supine position for sleeping for all infants except those few with specific medical conditions for which recommending a different position may be justified, in particular infants with apparent anatomical or functional upper airway compromise.

Many parents and healthcare providers were initially concerned that supine sleeping would be associated with an increase in adverse consequences, such as difficulty sleeping, vomiting, or aspiration. Evidence suggests that the risk of regurgitation and choking is highest for prone-sleeping infants. Some newborn nursery staff still tend to favor side positioning which models inappropriate infant care practice to parents. Infants sleeping on their backs do not have more episodes of cyanosis or apnea, and reports of apparent life-threatening events actually decreased in Scandinavia after increased use of the supine position. Among infants in the United States who maintained the same sleep position at 1, 3, and 6 mo of age, no clinical symptoms or reasons for outpatient visits (including fever, cough, wheezing, trouble breathing or sleeping, vomiting, diarrhea, or respiratory illness) were more common in infants sleeping supine or on their sides compared with infants sleeping prone. Three symptoms were actually less common in infants sleeping supine or on their sides: fever at 1 mo, stuffy nose at 6 mo, and trouble sleeping at 6 mo. Outpatient visits for ear infection were less common at 3 and 6 mo for infants sleeping supine and also less common at 3 mo for infants sleeping on their side. These results provide reassurance for parents and healthcare providers and should contribute to universal acceptance of supine as the safest and optimal sleep position for infants.

Soft sleep surfaces or bedding, such as comforters, pillows, sheepskins, polysytrene bean pillows, and older or softer mattresses are associated with increased risk of SIDS. Head and face covering by loose bedding, particularly heavy comforters, is also associated with increased risk. Overheating has been associated with increased risk for SIDS based on indicators such as higher room temperature, a febrile history, sweating, and excessive clothing or bedding. Some studies have identified an interaction between overheating and prone sleeping, with overheating increasing the risk of SIDS only when infants are sleeping prone. Higher external environmental temperatures have not been associated with increased SIDS incidence in the United States.

Several studies have implicated bed sharing as a risk factor for SIDS. Bed sharing is particularly hazardous when other children are in the same bed, when the parent is sleeping with an infant on a couch or other soft or confining sleeping surface, and when the mother smokes. Infants younger than 4 mo of age are at increased risk even when mothers are nonsmokers. A meta-analysis of 19 studies found that the low-risk infants (i.e., those who were breastfed and never exposed to cigarette smoke in utero or after birth) still had a 5-fold increased risk of SIDS until the age of 3 mo if bed sharing. Risk is also increased with longer duration of bed sharing during the night, whereas returning the infant to the infant’s own crib has not been associated with increased risk. Room sharing without bed sharing is associated with lower SIDS rates, and is therefore recommended.

Infant Feeding Care Practices and Exposures

It is currently believed that there is a protective effect of breastfeeding on SIDS, after taking into account confounding factors. A meta-analysis found that there was a 45% reduction in SIDS after adjusting for confounding variables and that this protective effect increased for exclusive breastfeeding compared with partial breastfeeding.

Pacifier (dummy) use is associated with a lower risk of SIDS in the majority of studies when used for last sleep. Although it is not known if this is a direct effect of the pacifier itself or from associated infant or parental behavior, there is increasing evidence that pacifier use even with dislodgment can increase the arousability of infants during sleep. Concerns have been expressed about recommending pacifiers as a means of reducing the risk of SIDS for fear of adverse consequences, particularly interference with breastfeeding. Well-designed studies have found no association between pacifiers and breastfeeding duration.

Upper respiratory tract infections have generally not been found to be an independent risk factor for SIDS, but these and other minor infections may still have a role in the causal pathway of SIDS when other risk factors are present. Risk for SIDS has been found to be increased after illness among prone sleepers, those who were heavily wrapped, and those whose heads were covered during sleep.

No adverse association between immunizations and SIDS has been found. Indeed, SIDS infants are less likely to be immunized than control infants and, in immunized infants, no temporal relationship between vaccine administration and death has been identified. In a meta-analysis of case-control studies that adjusted for potentially confounding factors, the risk of SIDS for infants immunized with diphteria, tetanus, and pertussis was half that for nonimmunized infants.

SIDS rates remain higher among Native Americans, Alaskan Natives, and African-Americans. This may be due, in part, to group differences in adopting supine sleeping or other risk-reduction practices. Greater efforts are needed to address this persistent disparity and to ensure that SIDS risk-reduction education reaches all parents and all other care providers, including other family members and personnel at daycare centers.

GENETIC RISK FACTORS

As summarized in Table 375-4, there are numerous genetic differences identified in SIDS infants compared to healthy infants and to infants dying from other causes. Polymorphisms occurring at higher incidence in SIDS compared to controls include at least 11 cardiac ion channelopathy genes that are proarrhythmic, 3 5-HT genes, 8 autonomic nervous system development genes, and 8 genes related to infection that are proinflammatory.

Multiple studies confirm the importance of a final common pathway that involves cardiac sodium or potassium channel dysfunction caused by direct or indirect disturbance resulting in either long QT syndrome (LQTS) or other arrhythmia associated with current dysfunction. LQTS is a known cause of sudden unexpected death in adults and
Pathogenetic pathway

Environmental influences

Respiratory acidosis

Membrane voltage

-120 mV

0 mV

1 μA

1 ms

Genotype

Mutant SCNS5A (S1103Y)

Molecular phenotype

Increased late I Na

Cellular phenotype

Prolonged action potential and early afterdepolarizations

Organ phenotype

Prolonged QT interval (upper trace, red); torsades de pointes arrhythmia (lower trace)

Clinical phenotype

Sudden death

Figure 375-1 An arrhythmogenic pathogenetic pathway for sudden infant death syndrome (SIDS) from patient genotype to clinical phenotype, with environmental influences noted. The genetic abnormality—in this instance, a polymorphism in the cardiac Na+ channel ‘SCNS5A’—causes a molecular phenotype of increased late Na+ current (I Na) under the influence of environmental factors such as acidosis. Interacting with other ion currents that may themselves be altered by genetic and environmental factors, the late Na+ current causes a cellular phenotype of prolonged action potential duration as well as early afterdepolarizations. Prolonged action potential in the cells of the ventricular myocardium and further interaction with environmental factors such as autonomic innervation, which, in turn, may be affected by genetic factors, produce a tissue-organ phenotype of a prolonged Q-T interval on the electrocardiogram (ECG) and torsades de pointes arrhythmia in the whole heart. If this is sustained or degenerates to ventricular fibrillation, the clinical phenotype of SIDS results. Environmental and multiple genetic factors can interact at many different levels to produce the characteristic phenotypes at the molecular, cellular, tissue, organ, and clinical levels. (From Makielski JC: SIDS: genetic and environmental influences may cause arrhythmia in this silent killer, J Clin Invest 116:297–299, 2006.)

Both LQTS and SQTS are proarrhythmic and associated with cardiac arrest and sudden death. The other cardiac ion-related channelopathy polymorphisms are also proarrhythmic, including Brugada syndrome (BrS1, BrS2), and catecholaminergic paroxysmal ventricular tachycardia (CPVT1). Collectively, these mutations in cardiac ion channels provide a lethal arrhythmogenic substrate in some infants at risk for SIDS (see Fig. 375-1) and may account for 10% or more of channelopathies that provide a lethal arrhythmogenic substrate in some infants at risk for SIDS (see Fig. 375-1) and may account for 10% or more of SIDS cases.

Impaired central respiratory regulation is an important biologic abnormality in SIDS and genetic polymorphisms have been identified in SIDS infants that affect both serotonergic and adrenergic neurons. Monoamine oxidase A metabolizes both of these neurotransmitters and a recent study has observed a high association between SIDS and low expression alleles in males, perhaps contributing to the higher incidence of SIDS in males. Many genes are involved in the control of 5-HT synthesis, storage, membrane uptake, and metabolism. Polymorphisms have been identified in the promoter region of the 5-HT transporter (5-HTT) protein gene that occur in greater frequency in SIDS than control infants. The long “L” allele increased effectiveness of the promoter and reduced extracellular 5-HT concentrations at nerve endings compared to the short “S” allele. White, African-American, and Japanese SIDS infants were more likely than ethnicity-matched controls to have the “L” (long) allele, and there was also a negative association between SIDS and the S/S genotype. The L/L genotype was associated with increased 5-HT transporters on neuroimaging and postmortem binding studies. However, in a large San Diego dataset of SIDS infants, no relationship was found between SIDS and the L allele or the LL genotype.

An association has also been observed between SIDS and a 5-HTT intron 2 polymorphism, which differentially regulate 5-HTT expression. There were positive associations between SIDS and the intron 2 genotype distributions in African-American infants compared to African-American controls. The human FEV gene is specifically expressed in central 5-HT neurons in the brain, with a predicted role in specification and maintenance of the serotonergic neuronal phenotype. An insertion mutation has been identified in intron 2 of the FEV gene, and the distribution of this mutation differs significantly in SIDS compared to control infants.

Molecular genetic studies in SIDS victims have also identified mutations pertinent to early embryologic development of the autonomic nervous system (Table 375-4). Eleven protein-changing mutations have been identified in 14 of 92 SIDS cases among the PHOX2a, RET, ECE1, TLX3, and EN1 genes. Only 1 of these mutations (TLX3) was found in 2 of 92 controls. African-American infants accounted for 10 of 11 mutations in SIDS infants and in both affected controls with protein-changing mutations. Eight polymorphisms in the PHOX2B gene occurred significantly more frequently in SIDS compared to control infants. One study has reported an association between SIDS and a distinct tyrosine hydroxylase gene (THO1) allele, which regulates gene expression and catecholamine production.

Genetic differences in SIDS infants compared to control infants have been reported for 2 complement C4 genes. Some SIDS infants have loss-of-function polymorphisms in the gene promoter region for IL-10, another anti-inflammatory cytokine. Among SIDS infants compared to living controls, sudden infant death was strongly associated with decreased IL-10 levels and hence could contribute to SIDS by delaying initiation of protective antibody production or reducing capacity to inhibit inflammatory cytokine production. Other studies have not found differences in IL-10 genes in SIDS compared to
control infants, but one study did identify an association with the ATA haplotype in sudden and unexpected infant deaths classified as resulting from infection.

Polymorphisms associated with proinflammatory responses have also been found more frequently in SIDS infants compared to controls. An association was observed between single-nucleotide polymorphisms in the proinflammatory gene encoding interleukin (IL)-8 and SIDS infants sleeping prone compared to SIDS infants found in other sleep positions. IL-1 is another proinflammatory gene, and a higher prevalence has been reported in SIDS infants of the IL-1 receptor antagonist (IL-1RN), which would predispose to higher risk from infection. Significant associations with SIDS are reported for polymorphisms in VEGF, IL-6, and tumor necrosis factor-α. These 3 cytokines are proinflammatory, and these gain-of-function polymorphisms would result in increased inflammatory response to infectious or inflammatory stimuli and hence contribute to an imbalance between proinflammatory and antiinflammatory cytokines. As apparent proof of principle, elevated levels of IL-6 and VEGF have been reported from cerebrospinal fluid in SIDS infants. There were no group differences in the IL6-174G/C polymorphism in a Norwegian SIDS study, but the aggregate evidence nevertheless suggests an activated immune system in SIDS and thus implicates genes involved in the immune system. Almost all SIDS infants in 1 study had positive histories for prone sleeping and fever prior to death and positive HLA-DR expression in laryngeal mucosa, and high HLA-DR expression was associated with high levels of IL-6 in cerebrospinal fluid.

Numerous reports have implicated polymorphisms in genes regulating energy production in SIDS infants, but the importance of these findings requires further study (Table 375-4). Of interest, cardiac arrhythmias, including prolonged QT intervals, have been observed in families with mitochondrial disease. However, the mitochondrial DNA polymorphism T3394C that is associated with cardiac arrhythmia has not been observed to occur with greater frequency in SIDS compared to control infants.

**GENE-AND-ENVIRONMENT INTERACTIONS**

Interactions between genetic and environmental risk factors determine the actual risk for SIDS in individual infants (Fig. 375-2). There appears to be an interaction between prone sleep position and impaired ventilatory and arousal responsiveness. Facedown or nearly facedown sleeping does occasionally occur in prone-sleeping infants, but normal healthy infants arouse before such episodes become life-threatening. Infants with insufficient arousal responsiveness to asphyxia, however, may be at risk for sudden death from resulting episodes of airway obstruction and asphyxia. There may also be links between modifiable risk factors such as soft bedding, prone sleep position, and thermal stress, and links between genetic risk factors such as ventilatory and arousal abnormalities and temperature or metabolic regulation deficits. Cardiorespiratory control deficits could be related to 5-HTTP polymorphisms, for example, or to polymorphisms in genes pertinent to autonomic nervous system development. Affected infants could be at increased risk for sleep-related hypoxemia and hence more susceptible to adverse effects associated with unsafe sleep position or bedding. Infants at increased risk for sleep-related hypoxemia could also be at greater risk for fatal arrhythmias in the presence of a cardiac ion channelopathy polymorphism.

In >50% of SIDS victims, recent febrile illnesses, often related to upper respiratory infection, have been documented (see Table 375-5). Otherwise benign infections might increase risk for SIDS if interacting with genetically determined impaired immune responses, including those resulting from partial deletions in the complement C4 gene or to interleukin polymorphisms (see Table 375-4). Deficient inflammatory responsiveness can also occur as a result of mast cell degranulation, which has been reported in SIDS infants; this is consistent with an anaphylactic reaction to a bacterial toxin, and some family members of SIDS infants also have mast cell hyperreleasability and degranulation, suggesting that increased susceptibility to an anaphylactic reaction is another genetic factor influencing fatal outcomes to otherwise minor infections in infants. Interactions between upper respiratory infections or other minor illnesses and other factors such as prone sleeping might also play a role in the pathogenesis of SIDS.

The increased risk for SIDS associated with fetal and postnatal exposure to cigarette smoke may be related at least in part to genetic or epigenetic factors, including those affecting brainstem autonomic control. Human infant studies document decreased ventilatory and arousal responsiveness to hypoxia following fetal nicotine exposure, and impaired autoregulation after apnea has been associated with postnatal nicotine exposure. Decreased brainstem immunoreactivity to selected protein kinase C and neuronal nitric oxide synthase isoforms occurs in rats exposed to cigarette smoke prenatally, another potential cause of impaired hypoxic responsiveness. Smoking exposure also increases susceptibility to viral and bacterial infections and increases bacterial binding after passive coating of mucosal surfaces with smoke components, implicating interactions between smoking, cardiorespiratory control, and immune status. Flavin-monoxygenase 3 (FMO3) is one of the enzymes that metabolizes nicotine, and a polymorphism has recently been identified that occurs more frequently in SIDS infants compared to controls and more frequently in infants whose mothers reported heavy smoking (Table 375-4). This polymorphism thus provides a potential genetic risk factor for SIDS in infants exposed to cigarette smoke.

In infants with a cardiac ion channelopathy, risk for a fatal arrhythmia during sleep may be substantially enhanced by predisposing perturbations that increase electrical instability. These perturbations could include REM sleep with bursts of vagal and sympathetic activation, minor respiratory infections, or any other cause of sleep-related hypoxemia or hypercarbia, especially those resulting in acidosis. The prone sleeping position is associated with increased sympathetic activity.

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**INFANT GROUPS AT INCREASED RISK FOR SUDDEN INFANT DEATH SYNDROME**

**Unexplained Apparent Life-Threatening Events**

Infants with an unexplained apparent life-threatening event (ALTE) are at increased risk for SIDS. An ALTE is defined as an episode that frightens an observer and manifests with some combination of central, obstructive, or mixed apnea; cyanotic, pallid, plethora, erythematous, color change; hypotonia (rarely hypertonia); and choking or gasping. A history of an unexplained ALTE has been reported in 5-9% of SIDS victims, and the risk of SIDS appears to be higher with 2 or more
unexplained events, but no definitive incidence rates are available. Compared with healthy control infants, the risk for SIDS may be as much as 3-5 times greater in infants having experienced an ALTE. Although most studies of ALTE have not specified gestational age, 30% of ALTE infants in the Collaborative Home Infant Monitoring Evaluation were ≤37 wk gestation at birth.

Subsequent Siblings of a Sudden Infant Death Syndrome Victim

The next-born siblings of first-born infants dying of any noninfectious natural cause are at significantly increased risk for infant death from the same cause, including SIDS. The relative risk is 9.1 for the same cause of recurrent death vs 1.6 for a different cause of death. The relative risk for recurrent SIDS (range: 5.4-5.8) is similar to the relative risk for non-SIDS causes of recurrent death (range: 4.6-12.5). The risk for recurrent infant mortality from the same cause as in the index sibling thus appears to be increased to a similar degree in subsequent siblings for both explained causes and for SIDS. This increased risk for recurrent SIDS in families is consistent with genetic risk factors interacting with environmental risk factors (see Tables 375-4 and 375-5 and Fig. 375-2).

Prematurity

Despite reductions in SIDS and SUID among infants born preterm by more than 50% since initiation of the back-to-sleep campaign in the United States 20 yr ago, the risk for death remains significantly higher than for infants born full term. This increased risk is likely related in part to immaturity of brainstem ventilatory control. Also, although the environmental risk factors for SIDS and SUID are qualitatively similar to those in full-term infants, including nonsupine sleeping position and other unsafe sleep practices, infants born preterm do have more sociodemographic risk factors overall than infants born at term. Among all gestational age groups, the postnatal age of death from SIDS and other SUID progressively decreases as gestational age at birth increases, and the postmenstrual age at death progressively increases as gestational age at birth increases. Compared with infants born at 37-42 wk, the odds ratio for SIDS is greatest for infants born at 24-28 wk gestation (2.57, 95% confidence interval 2.08, 3.17). The odds ratio progressively decreases as gestational age at birth increases, but even at 33-36 wk gestational age at birth remains significantly increased compared to infants born at term.

Physiologic Studies

Physiologic studies have been performed in healthy infants in early infancy, a few of whom later died of SIDS. Physiologic studies have also been performed on infant groups at increased risk for SIDS, especially those with ALTE and subsequent siblings of SIDS. In the aggregate, these studies have indicated brainstem abnormalities in neuroregulation of cardiorespiratory control or other autonomic functions and are consistent with the autopsy findings and genetic studies in SIDS victims (see “Pathology” and “Genetic Risk Factors” above). In addition to chemoreceptor sensitivity, these observed physiologic abnormalities also include respiratory patterns, control of heart and respiratory rate or variability, and asphyxic arousal responsiveness. A deficit in arousal responsiveness may be a necessary prerequisite for SIDS to occur but may be insufficient to cause SIDS in the absence of other genetic or environmental risk factors. Autoresuscitation (gasing) is a critical component of the asphyxic arousal response, and a failure of autoresuscitation in SIDS infants may be the final and most devastating physiologic failure. Most normal full-term infants younger than 9 postnatal wk of age in 1 study aroused in response to mild hypoxia, but only 10-15% aroused if older than 9 wk of age. These data thus suggest that ability to arouse to mild to moderate hypoxic stimuli may be at a nadir at the age range of greatest risk for SIDS.

The ability to shorten the QT interval as heart rate increases appears to be impaired in some SIDS victims, suggesting that such infants may be predisposed to ventricular arrhythmia. This is consistent with the observations of cardiac ion channel gene polymorphisms in other SIDS victims (see Table 375-4), but there are no antemortem QT interval data in the SIDS infants having postmortem channelopathy polymorphisms. Infants studied physiologically and dying of SIDS a few weeks later had higher heart rates in all sleep–wake states, diminished heart rate variability during wakefulness, and significantly lower heart rate variability at the respiratory frequency across all sleep–wake cycles. Also, these SIDS infants had longer QT intervals than control infants in both REM and non-REM sleep, especially in the late hours of the night when most SIDS likely occurs. In only 1 of these SIDS infants, however, did the QT interval exceed 440 milliseconds.

Part of the decreased heart rate variability and increased heart rate observed in infants who later died of SIDS may have been related to decreased vagal tone, perhaps at least in part related to vagal neuropathy or to brainstem damage in areas responsible for parasympathetic cardiac control. In a comparison of heart rate power spectra before and after obstructive apneas in clinically asymptomatic infants, infants later dying of SIDS did not have the decreases in low-frequency to high-frequency power ratios observed in infants who survived. Some future SIDS victims thus have different autonomic responsiveness to obstructive apnea, perhaps indicating impaired autonomic nervous system control associated with higher vulnerability to external or endogenous stress factors and hence to reduced electrical stability of the heart.

Home cardiorespiratory monitors with memory capability have recorded the terminal events in some SIDS victims. These recordings did not include pulse oximetry and could not identify obstructed breaths due to reliance on transthoracic impedance for breath detection. In most instances, there has been sudden and rapid progression of severe bradycardia that was either unassociated with central apnea or appeared to occur too soon to be explained by the central apnea. These observations are consistent with an abnormality in autonomic control of heart rate variability, or with obstructed breaths resulting in bradycardia or hypoxemia and associated with impaired autoresuscitation or arousal.

CLINICAL STRATEGIES

Home Monitoring

SIDS cannot be prevented in individual infants because it is not possible to identify prospective SIDS infants, and no effective intervention has been established even if SIDS infants could be prospectively identified. Studies of cardiorespiratory pattern or other autonomic abnormalities do not have sufficient sensitivity and specificity to be clinically useful as screening tests. Home electronic surveillance using existing technology does not reduce the risk of SIDS. Although a prolonged QT interval in an infant may be treated if diagnosed, neither the role of routine postnatal electrocardiographic screening, the cost-effectiveness of diagnosis and treatment, nor the safety of treatment in infants has been established (see Chapter 429). Parental electrocardiographic screening is not helpful because spontaneous mutations are common.

Reducing the Risk of Sudden Infant Death Syndrome

Reducing risk behaviors and increasing protective behaviors among infant caregivers to achieve further reductions and eventual elimination of SIDS is a critical goal. Recent plateaus in placing infants supine for sleep in the United States at approximately 75% for all races and only 56% for African-Americans are cause for concern and require renewed educational efforts. The American Academy of Pediatrics guidelines to reduce the risk of SIDS were updated in 2011 and expanded to include reducing the risk of all sudden and unexpected sleep-related infant deaths. The guidelines are appropriate for most infants, but physicians and other healthcare providers might, on occasion, need to consider alternative approaches. The major components of the American Academy of Pediatrics guidelines are:

- Full-term and premature infants should be placed for sleep in the supine position. There are no adverse health outcomes from supine sleeping. Side sleeping is not recommended.
- It is recommended that infants sleep in the same room as their parents but in their own crib or bassinet that conforms to the

Placing the crib or bassinette near the mother’s bed facilitates nursing and contact.

- Infants should be put to sleep on a firm mattress. Waterbeds, sofas, soft mattresses, or other soft surfaces should not be used. In addition, car seats, strollers, swings and other sitting devices should not be used for sleeping. Sleeping in an upright position can lead to gastroesophageal reflux or upper airway obstruction from head flexion.

- Soft materials in the infant’s sleep environment—over, under, or near the infant—should be avoided. These include pillows, comforters, quilts, sheepskins, bumper pads, and stuffed toys. Because loose bedding may be hazardous, blankets, if used, should be tucked in around the crib mattress. Sleeping clothing, such as a sleep sack, can be used in place of blankets.

- Avoid overheating and overbundling. The infant should be lightly clothed for sleep and the thermostat set at a comfortable temperature.

- Infants should be immunized in accordance with recommendations of the American Academy of Pediatrics and the Centers for Disease Control and Prevention. There is no evidence that immunizations increase risk for SIDS. Indeed, recent evidence suggests that immunizations may have a protective effect against SIDS.

- Healthcare professionals, staff in newborn nurseries and neonatal intensive care units, and child care providers should adopt the SIDS reduction recommendations beginning at birth.

- Infants should have some time in the prone position (tummy time) while awake and observed. Alternating the placement of the infant’s head as well as his or her orientation in the crib can also minimize the risk of head flattening from supine sleeping (positional plagiocephaly).

- Devices advertised to maintain sleep position, “protect” a bed-sharing infant, or reduce the risk of rebreathing are not recommended.

- Home cardiorespiratory and/or oxygen saturation monitoring may be of value for selected infants who have extreme instability, but there is no evidence that monitoring decreases the incidence of SIDS and it is therefore not recommended for this purpose.

- Breastfeeding is recommended. If possible, mothers should exclusively breastfeed or feed with expressed human milk until the infant is 6 mo of age.

- If a breastfeeding mother brings the infant into the adult bed for nursing, the infant should be returned to a separate sleep surface when the mother is ready for sleep.

- Consider offering a pacifier at bedtime and naptime. The pacifier should be used when placing the infant down for sleep and need not be reinserted once it falls out. For breastfed infants, delay introduction of the pacifier until breastfeeding is well established.

- Mothers should not smoke, drink alcohol, or use illicit drugs during pregnancy or after birth, and infants should not be exposed to secondhand smoke.

- The national Back to Sleep campaign should be expanded to emphasize the multiple characteristics of a safe sleeping environment and to focus on the groups with continuing higher rates of SIDS. Educational strategies must be tailored to each racial or ethnic group to ensure acceptance within that cultural context. Secondary care providers need to be targeted to receive these educational messages, including daycare providers, grandparents, foster parents, and babysitters.

- Research and surveillance should be continued on the risk factors, causes and pathophysiological mechanisms of SIDS and other sleep-related SUID, with the ultimate goal of preventing these deaths entirely. Federal and private funding agencies need to remain committed to this research.

Bibliography is available at Expert Consult.
NORMAL NEWBORN NOSE

In contrast to children and adults who preferentially breathe through their nose unless nasal obstruction interferes, most newborn infants are obligate nasal breathers and significant nasal obstruction presenting at birth, such as choanal atresia, may be a life-threatening situation for the infant unless an alternative to the nasal airway is established. Nasal congestion with obstruction is common in the 1st yr of life and can affect the quality of breathing during sleep; it may be associated with a narrow nasal airway, viral or bacterial infection, enlarged adenoids, or maternal estrogenic stimuli similar to rhinitis of pregnancy. The internal nasal airway doubles in size in the 1st 6 mo of life, leading to resolution of symptoms in many infants. Supportive care with a bulb syringe and saline nose drops, topical nasal decongestants, and antibiotics, when indicated, improve symptoms in affected infants.

PHYSIOLOGY

The nose is responsible for the initial warming and humidification of inspired air and olfaction. In the anterior nasal cavity, turbulent airflow and coarse hairs enhance the deposition of large particulate matter; the remaining nasal airways filter out particles as small as 6 µm in diameter. In the turbinate region, the airflow becomes laminar and the airstream is narrowed and directed superiorly, enhancing particle deposition, warming, and humidification. Nasal passages contribute as much as 50% of the total resistance of normal breathing. Nasal flaring, a sign of respiratory distress, reduces the resistance to inspiratory airflow through the nose and can improve ventilation (see Chapter 373). Although the nasal mucosa is more vascular (especially in the turbinate region) than in the lower airways, the surface epithelium is similar, with ciliated cells, goblet cells, submucosal glands, and a covering blanket of mucus. The nasal secretions contain lysozyme and secretory immunoglobulin (Ig) A, both of which have antimicrobial activity, and IgG, IgE, albumin, histamine, bacteria, lactoferrin, and cellular debris, as well as mucous glycoproteins, which provide viscoelastic properties. Aided by the ciliated cells, mucus flows toward the nasopharynx, where the airstream widens, the epithelium becomes squamous, and secretions are wiped away by swallowing. Replacement of the mucous layers occurs about every 10-20 min. Estimates of daily mucus production vary from 0.1-0.3 mg/kg/24 hr, with most of the mucus being produced by the submucosal glands.

CONGENITAL DISORDERS

Congenital structural nasal malformations are uncommon compared with acquired abnormalities. The nasal bones can be congenitally absent so that the bridge of the nose fails to develop, resulting in nasal hypoplasia. Congenital absence of the nose (arhinia), complete or partial duplication, or a single centrally placed nostril can occur in isolation but is usually part of a malformation syndrome. Rarely,
supernumerary teeth are found in the nose, or teeth grow into it from the maxilla.

Nasal bones can be sufficiently malformed to produce severe narrowing of the nasal passages. Often, such narrowing is associated with a high and narrow hard palate. Children with these defects can have significant obstruction to airflow during infections of the upper airways and are more susceptible to the development of chronic or recurrent hypoventilation (see Chapter 19). Rarely, the alae nasi are sufficiently thin and poorly supported to result in inspiratory obstruction, or there may be congenital nasolacrimal duct obstruction with cystic extension into the nasopharynx, causing respiratory distress.

**CHOANAL ATRESIA**

This is the most common congenital anomaly of the nose and has a frequency of approximately 1 in 7,000 live births. It consists of a unilateral or bilateral bony (90%) or membranous (10%) septum between the nose and the pharynx; most cases are a combination of bony and membranous atresia. The pathogenesis is unknown but theories include persistence of the bucopharyngeal membranes or failure of the oronasal membrane to rupture. The unilateral defect is more common and the female: male ratio is approximately 2:1. Approximately 50-70% of affected infants have other congenital anomalies (CHARGE syndrome, Treacher-Collins, Kallmann syndrome, VATER [vertebral defects, imperforate anus, tracheoesophageal fistula, and renal defects] association, Pfeiffer syndrome), with the anomalies occurring more often in bilateral cases. The CHARGE syndrome (coloboma, heart disease, atresia choanae, retarded growth and development or central nervous system anomalies or both, genital anomalies or hypogonadism or both, and ear anomalies or deafness or both) is one of the more common anomalies associated with choanal atresia—approximately 10-20% of patients with choanal atresia have it. Most patients with CHARGE syndrome have mutations in the CHD7 gene, which is involved in chromatin organization.

**Clinical Manifestations**

Newborn infants have a variable ability to breathe through their mouths, so nasal obstruction does not produce the same symptoms in every infant. When the obstruction is unilateral, the infant may be asymptomatic for a prolonged period, often until the first respiratory infection, when unilateral nasal discharge or persistent nasal obstruction can suggest the diagnosis. Infants with bilateral choanal atresia who have difficulty with mouth breathing make vigorous attempts to inspire, often suck in their lips, and develop cyanosis. Distressed children then cry (which relieves the cyanosis) and become calmer, with normal skin color, only to repeat the cycle after closing their mouths. Those who are able to breathe through their mouths at once experience difficulty when sucking and swallowing, becoming cyanotic when they attempt to feed.

**Diagnosis**

Diagnosis is established by the inability to pass a firm catheter through each nostril 3-4 cm into the nasopharynx. The atretic plate may be seen directly with fiberoptic rhinoscopy. The anatomy is best evaluated by using high-resolution CT (Fig. 376-1).

**Treatment**

Initial treatment consists of prompt placement of an oral airway, maintaining the mouth in an open position, or intubation. A standard oral airway (such as that used in anesthesia) can be used, or a feeding nipple can be fashioned with large holes at the tip to facilitate air passage. Once an oral airway is established, the infant can be fed by gavage until breathing and eating without the assisted airway is possible. In bilateral cases, intubation or, less often, tracheotomy may be indicated. If the child is free of other serious medical problems, operative intervention is considered in the neonate; transnasal repair is the treatment of choice, with the introduction of small magnifying endoscopes and smaller surgical instruments and drills. Stents are usually left in place for weeks after the repair to prevent closure or stenosis. Tracheotomy should be considered in cases of bilateral atresia in which the child has other potentially life-threatening problems and in whom early surgical repair of the choanal atresia may not be appropriate or feasible. Operative correction of unilateral obstruction may be deferred for several years. In both unilateral and bilateral cases, restenosis necessitating dilation or reoperation, or both, is common. Mitomycin C has been used to help prevent the development of granulation tissue and stenosis.

**CONGENITAL DEFECTS OF THE NASAL SEPTUM**

Perforation of the septum is most commonly acquired after birth secondary to infection, such as syphilis or tuberculosis, or trauma; rarely, it is developmental. Continuous positive airway pressure canulas are a cause of iatrogenic perforation. Trauma from delivery is the most common cause of septal deviation noted at birth. When recognized early, it can be corrected with immediate realignment using blunt probes, cotton applicators, and topical anesthesia. Formal surgical correction, when required, is usually postponed to avoid disturbance of midface growth.

**Mild septal deviations** are common and usually asymptomatic; abnormal formation of the septum is uncommon unless other malformations are present, such as cleft lip or palate.

**PYRIFORM APERTURE STENOSIS**

Infants with this bony abnormality of the anterior nasal aperture present at birth or shortly thereafter with severe nasal obstruction leading to noisy breathing and respiratory distress that worsen with feeding and improve with crying. It can occur in isolation or in association with other malformations including holoprosencephaly.
primarily CT scan. In the case of surgically correctable congenital problems such as choanal atresia, surgery is performed once the child is deemed healthy and free of life-threatening problems such as congenital heart disease.

Bibliography is available at Expert Consult.

hypopituitarism, and cardiac and urogenital malformations. Diagnosis is made by CT of the nose (Fig. 376-2). Medical management (nasal decongestants, humidification, nasopharyngeal airway insertion, management of reflux) can be used but surgical repair by means of an anterior, sublabial approach may be needed if the child cannot feed or breathe without difficulty. A drill is used to enlarge the stenotic anterior bone apertures.

CONGENITAL MIDLINE NASAL MASSES

Dermoids, gliomas, and encephaloceles (in descending order of frequency) occur intranasally or extranasally and can have intracranial connections or extend intracraniawith communication to the subarachnoid space. The theory for the embryologic development of congenital midline nasal masses is faulty retraction of the dural diverticulum. Dermoids and epidermoids are the most common type of congenital midline nasal mass and have been reported to represent up to 61% of lesions. Nasal dermoids often have a dimple or pit on the nasal dorsum, sometimes with hair being present, and can predispose to intracranial infections if an intracranial fistula or sinus is present. Recurrent infection of the dermoid itself is more common. Gliomas or heterotopic brain tissue are firm, whereas encephaloceles are soft and enlarge with crying or the Valsalva maneuver. Diagnosis is based on physical examination findings and results from imaging studies. CT provides the best bony detail, but MRI is helpful also because of its superior ability to define intracranial extension (Fig. 376-3). Surgical excision of these masses is generally required, with the extent and surgical approach based on the type and size of the mass.

Other nasal masses include hemangiomas, congenital nasolacrimal duct obstruction (which can occur as an intranasal mass), nasal polyps, and tumors such as rhabdomyosarcoma (see Chapter 500). Nasal polyps are rarely present at birth, but the other masses often present at birth or in early infancy (see Chapter 378).

Poor development of the paranasal sinuses and a narrow nasal airway are associated with recurrent or chronic upper airway infection in Down syndrome (see Chapter 81).

DIAGNOSIS AND TREATMENT

In children with congenital nasal disorders, supportive care of the airway is given until the diagnosis is established. Diagnosis is made through a combination of flexible scoping and imaging studies,
Bibliography
Tumors, septal perforations, and other acquired abnormalities of the nose and paranasal sinuses can manifest with epistaxis. Midface trauma with a nasal or facial fracture may be accompanied by epistaxis. Trauma to the nose can cause a septal hematoma; if treatment is delayed, this can lead to necrosis of septal cartilage and a resultant saddle-nose deformity. Other abnormalities that can cause a change in the shape of the nose and paranasal bones, with obstruction but few other symptoms, include fibroosseous lesions (ossifying fibroma, fibrous dysplasia, cementifying fibroma) and mucoceles of the paranasal sinuses. These conditions may be suspected on physical examination and confirmed by CT scan and biopsy. Although these are considered benign lesions, they can all greatly change the anatomy of surrounding bony structures and often require surgical intervention for management.

377.1 Foreign Body

ETIOLOGY

Foreign bodies (food, beads, crayons, small toys, erasers, paper wads, buttons, batteries, beans, stones, pieces of sponge, and other small objects) are often placed in the nose by small children and developmentally delayed children and constitute ≤1% of pediatric emergency department visits. Nasal foreign bodies can go unrecognized for long periods of time because they initially produce few symptoms and
are difficult to visualize. First symptoms include unilateral obstruction, sneezing, relatively mild discomfort, and, rarely, pain. Presenting clinical symptoms include history of insertion of foreign bodies (86%), mucopurulent nasal discharge (24%), foul nasal odor (9%), epistaxis (6%), nasal obstruction (3%), and mouth breathing (2%). Irritation results in mucosal swelling because some foreign bodies are hydroscopic and increase in size as water is absorbed; signs of local obstruction and discomfort can increase with time. The patient might also present with a generalized body odor known as bromhidrosis.

**DIAGNOSIS**

Unilateral nasal discharge and obstruction should suggest the presence of a foreign body, which can often be seen on examination with a nasal speculum or wide otoscope placed in the nose. Purulent secretions may have to be cleared so that the foreign object can actually be seen; a headlight, suction, and topical decongestants are often needed. The object is usually situated anteriorly, but unskilled attempts at removal can force the object deeper into the nose. A long-standing foreign body can become embedded in granulation tissue or mucosa and appear as a nasal mass. A lateral skull radiograph assists in diagnosis if the foreign body is metallic or radiopaque.

**TREATMENT**

A quick examination of the nose is made to determine if a foreign body is present, and whether it needs to be removed emergently. Planning is then made for office or operating room extraction of the foreign body. Prompt removal minimizes the danger of aspiration and local tissue necrosis. This can usually be performed with topical anesthesia, using either forceps or nasal suction. Alternatively, a Katz catheter (made specifically for the removal of foreign bodies from the nose and ear) can be inserted above and distal to the object, inflated, and drawn back with gentle traction. The “mother kiss” approach has been successful in acute situations where a person occludes the unaffected nostril and then, with a complete seal over the child’s mouth attempts to dislodge the foreign body by blowing into the mouth. A similar approach uses an Ambu bag over the mouth with the unaffected nostril occluded. If there is marked swelling, bleeding, or tissue overgrowth, general anesthesia may be needed to remove the object. Infection usually clears promptly after the removal of the object and, generally, no further therapy is necessary. Magnets can be used to extract metal foreign bodies, 2% lidocaine can be used to kill live insects before removal, and irrigation should be avoided with vegetable matter or sponges because of the risk of foreign-body swelling.

**COMPLICATIONS**

Serious complications include posterior dislodgment and aspiration, trauma caused by the object itself or removal attempts, infection, and choanal stenosis. Infection is common and gives rise to a purulent, malodorous, or bloody discharge. Local tissue damage from long-standing foreign body, or alkaline injury from a disk battery, can lead to local tissue loss and cartilage destruction. A synechia or scar band can then form, causing nasal obstruction. Loss of septal mucosa and cartilage can cause a septal perforation. Disk batteries are especially dangerous when placed in the nose; they leach base, which causes pain and local tissue destruction in a matter of hours. Magnets also carry a risk of septal perforation and necrosis.

Tetanus is a rare complication of long-standing nasal foreign bodies in nonimmunized children (see Chapter 211). Toxic shock syndrome is also rare and most commonly occurs from nasal surgical packing (see Chapter 181.2); oral antibiotics should be administered when nasal surgical packing is placed.

**PREVENTION**

Tempting objects, such as round, shiny beads, should only be used under adult supervision. Disk batteries should be stored away from the reach of small children.

Bibliography is available at Expert Consult.

### 377.2 Epistaxis

*Joseph Haddad Jr. and Sarah Keesecker*

Although rare in infancy, nosebleeds are common in children older than 2 yr of age. Their incidence decreases after puberty. Diagnosis and treatment depend on the location and cause of the bleeding.

**ANATOMY**

The most common site of bleeding is the Kiesselbach plexus, an area in the anterior septum where vessels from both the internal carotid (anterior and posterior ethmoid arteries) and external carotid (sphenopalatine and terminal branches of the internal maxillary arteries) converge. The thin mucosa in this area, as well as the anterior location, make it prone to exposure to dry air and trauma.

**ETIOLOGY**

Epistaxis can be classified into primary or secondary based on cause and this has implications for diagnosis and management. Common causes of nosebleeds from the anterior septum include digital trauma, foreign bodies, dry air, and inflammation, including upper respiratory tract infections, sinusitis, and allergic rhinitis (Table 377-1). There is often a family history of childhood epistaxis. Nasal steroid sprays are commonly used in children, and their chronic use may be associated with nasal mucosal bleeding. Young infants with significant gastroesophageal reflux into the nose rarely present with epistaxis secondary to mucosal inflammation. Susceptibility is increased during respiratory infections and in the winter when dry air irritates the nasal mucosa, resulting in formation of fissures and crusting. Severe bleeding may be encountered with congenital vascular abnormalities, such as hereditary hemorrhagic telangiectasia (see Chapter 432.3), varicosities, hemangio mas, and, in children with thrombocytopenia, deficiency of clotting factors, particularly von Willebrand disease (see Chapter 477), hypertension, renal failure, or venous congestion. Recurrent epistaxis despite cauterezation is associated with mild coagulation disorders. The family history may be positive for abnormal bleeding (epistaxis or other sites); specific testing for von Willebrand disease is indicated because the prothrombin time or partial thromboplastin time may be normal despite having a bleeding disorder. Nasal polyps or other intranasal growths may be associated with epistaxis. Recurrent, and often severe, nosebleeds may be the initial presenting symptom in juvenile nasal angiofibroma, which occurs in adolescent boys.

#### Table 377-1 Possible Causes of Epistaxis

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis digitorum (nose picking)</td>
</tr>
<tr>
<td>Rhinitis (allergic or viral)</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
</tr>
<tr>
<td>Foreign bodies</td>
</tr>
<tr>
<td>Intranasal neoplasm or polyps</td>
</tr>
<tr>
<td>Irritants (e.g., cigarette smoke)</td>
</tr>
<tr>
<td>Septal deviation</td>
</tr>
<tr>
<td>Septal perforation</td>
</tr>
<tr>
<td>Trauma including child abuse</td>
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<tr>
<td>Vascular malformation or telangiectasia</td>
</tr>
<tr>
<td>Hemophilia</td>
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<tr>
<td>von Willebrand disease</td>
</tr>
<tr>
<td>Platelet dysfunction</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Liver disease (e.g., cirrhosis)</td>
</tr>
<tr>
<td>Medications (e.g., aspirin, anticoagulants, nonsteroidal antiinflammatory drugs, topical corticosteroids)</td>
</tr>
<tr>
<td>Cocaine abuse</td>
</tr>
</tbody>
</table>

Bibliography
CLINICAL MANIFESTATIONS
Epistaxis usually occurs without warning, with blood flowing slowly but freely from 1 nostril or occasionally from both. In children with nasal lesions, bleeding might follow physical exercise. When bleeding occurs at night, the blood may be swallowed and become apparent only when the child vomits or passes blood in the stools. Posterior epistaxis can manifest as anterior nasal bleeding or, if bleeding is copious, the patient might vomit blood as the initial symptom.

TREATMENT
Most nosebleeds stop spontaneously in a few minutes. The nares should be compressed and the child kept as quiet as possible, in an upright position with the head tilted forward to avoid blood trickling back into the throat. Cold compresses applied to the nose can also help. If these measures do not stop the bleeding, local application of a solution of oxymetazoline (Afrin or Neo-Synephrine) (0.25-1%) may be useful. If bleeding persists, an anterior nasal pack may need to be inserted; if bleeding originates in the posterior nasal cavity, combined anterior and posterior packing is necessary. After bleeding is under control, and if a bleeding site is identified, its obliteration by cautery with silver nitrate may prevent further difficulties. Because the septal cartilage derives its nutrition from the overlying mucoperichondrium, only 1 side of the septum should be cauterized at a time to reduce the chance of a septal perforation. During the winter, or in a dry environment, a room humidifier, saline drops, and petrolatum (Vaseline) applied to the septum can help to prevent epistaxis. Antiseptic cream (e.g., mupirocin) significantly increases the proportion of children who have complete resolution of bleeding at 8 wk compared to no treatment. Ointments prevent infection, increase moisture, decrease bleeding, and are commonly used in clinical practice. However, the combination of silver nitrate cautery and antiseptic nasal cream is superior to antiseptic cream alone. Patients with severe epistaxis despite conservative medical measures should be considered for surgical ligation techniques or embolization. In patients with severe or repeated epistaxis, blood transfusions may be necessary. Otolaryngologic evaluation is indicated for these children and for those with bilateral bleeding or with hemorrhage that does not arise from the Kiesselbach plexus. Secondary epistaxis should be managed by identification of the cause, application of appropriate nasal therapy, and correct systemic medical management. Hematologic evaluation (for coagulopathy and anemia), along with nasal endoscopy and diagnostic imaging, may be needed to make a definitive diagnosis in cases of severe recurrent epistaxis. Replacement of deficient clotting factors may be required for patients who have an underlying hematologic disorder (see Chapter 476). Profuse unilateral epistaxis associated with a nasal mass in an adolescent boy near puberty might signal a juvenile nasopharyngeal angiofibroma. This unusual tumor has also been reported in a 2 yr old and in 30-40 yr olds, but the incidence peaks in adolescent and preadolescent boys. CT with contrast medium enhancement and MRI are part of the initial evaluation; arteriography, embolization, and extensive surgery may be needed.

Surgical intervention may also be needed for bleeding from the internal maxillary artery or other vessels that can cause bleeding in the posterior nasal cavity.

PREVENTION
The discouragement of nose picking, and attention to proper humidification of the bedroom during dry winter months helps to prevent many nosebleeds. Prompt attention to nasal infections and allergies is beneficial to nasal hygiene. Prompt cessation of nasal steroid sprays prevents ongoing bleeding.

Bibliography is available at Expert Consult.
Bibliography
Nasal Polyps
Joseph Haddad Jr. and Sarah Keesecker

ETIOLOGY
Nasal polyps are benign pedunculated tumors formed from edematous, usually chronically inflamed nasal mucosa. They commonly arise from the ethmoidal sinus and occur in the middle meatus. Occasionally, they appear within the maxillary antrum and can extend to the nasopharynx (antrochoanal polyp).

It is estimated that between 0.2% and 1% of the population will develop nasal polyps at some time; the incidence of nasal polyps increases with age. Antrochoanal polyps represent only 4-6% of all nasal polyps in the general population but account for approximately one-third of polyps in the pediatric population. Large or multiple polyps can completely obstruct the nasal passage. The polyps originating from the ethmoidal sinus are usually smaller and multiple, as compared with the large and usually single antrochoanal polyp.

Cystic fibrosis (CF; see Chapter 403) is the most common childhood cause of nasal polyposis and up to 50% of CF patients experience obstructing nasal polyposis, which is rare in non-CF children. Therefore, CF should be suspected in any child younger than 12 yr old with nasal polyps, even in the absence of typical respiratory and digestive symptoms. Cystic fibrosis patients with homozygosity for F508del and other severe mutations appear to have an elevated risk of nasal polyps. Nasal polyposis is also associated with chronic sinusitis (see Chapter 380) and allergic rhinitis. In the Samter triad, nasal polyps are associated with aspirin sensitivity and asthma; this condition is rare.

CLINICAL MANIFESTATIONS
Obstruction of nasal passages is prominent, with associated hyponasal speech and mouth breathing. Profuse unilateral mucoid or mucopurulent rhinorrhea may also be present. An examination of the nasal passages shows glistening, gray, grape-like masses squeezed between the nasal turbinates and the septum.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS
Examination of the external nose and rhinoscopy is performed. Ethmoidal polyps can be readily distinguished from the well-vascularized turbinate tissue, which is pink or red; antrochoanal polyps may have a more fleshy appearance (Fig. 378-1). Antrochoanal polyps may prolapse into the nasopharynx; flexible nasopharyngoscopy can assist in

making this diagnosis. Prolonged presence of ethmoidal polyps in a child can widen the bridge of the nose and erode adjacent osseous structures. Tumors of the nose cause more local destruction and distortion of the anatomy. CT scan of the midface is key to diagnosis and planning for surgical treatment (Fig. 378-2).

**TREATMENT**

Local or systemic decongestants are not usually effective in shrinking the polyps, although they may provide symptomatic relief from the associated mucosal edema. Intranasal steroid sprays, and sometimes systemic steroids, can provide some shrinkage of nasal polyps with symptomatic relief and have proved useful in children with CF and adults with nasal polyps. Topical nasal steroid therapy, fluticasone, mometasone, and budesonide appears to result in nasal symptom improvement. Doxycycline (200 mg on the 1st day followed by 100 mg daily) has a significant effect on the size of nasal polyps, nasal symptoms, and mucosal and systemic markers of inflammation. Polyps should be removed surgically if complete obstruction, uncontrolled rhinorrhea, or deformity of the nose appears. If the underlying pathogenic mechanism cannot be eliminated (such as CF), the polyps may soon return. Functional endoscopic sinus surgery provides more complete polyp removal and treatment of other associated nasal disease; in some cases, this has reduced the need for frequent surgeries. Nasal steroid sprays should also be started preventively, once postsurgical healing occurs.

Antrochoanal polyps do not respond to medical measures and must be removed surgically. Because these types of polyps are not associated with any underlying disease process, the recurrence rate is much less than for other types of polyps.


*Bibliography is available at Expert Consult.*
Bibliography


The common cold is an acute viral infection of the upper respiratory tract in which the symptoms of rhinorrhea and nasal obstruction are prominent. Systemic symptoms and signs such as headache, myalgia, and fever are absent or mild. The common cold is frequently referred to as infectious rhinitis but may also include self-limited involvement of the sinus mucosa and is more correctly termed rhinosinusitis.

**ETIOLOGY**

The most common pathogens associated with the common cold are the more than 200 types of human rhinoviruses (see Chapter 263), but the syndrome can be caused by many different virus families (Table 379-1). Rhinoviruses are associated with more than 50% of colds in adults and children. In young children, other viral etiologies of the common cold include respiratory syncytial virus (RSV; see Chapter 260), human metapneumovirus (see Chapter 261), parainfluenza viruses (see Chapter 259), and adenoviruses (see Chapter 262). Common cold symptoms may also be caused by influenza viruses, nonpolio enteroviruses, and human coronaviruses. Many viruses that cause rhinitis are also associated with other symptoms and signs such as cough, wheezing, and fever.

**EPIDEMIOLOGY**

Colds occur year-round, but the incidence is greatest from the early fall until the late spring, reflecting the seasonal prevalence of the viral pathogens associated with cold symptoms. In the northern hemisphere, the highest incidence of rhinovirus infection occurs in the early fall (August-October) and in the late spring (April-May). The seasonal incidence for parainfluenza viruses usually peaks in the late fall and late spring and is highest between December and April for RSVs, influenza viruses, human metapneumoviruses, and coronaviruses. Adenoviruses are detected at a low prevalence throughout the cold season, and enteroviruses may also be detected during summer months or throughout the year.

Young children have an average of 6-8 colds per year, but 10-15% of children have at least 12 infections per year. The incidence of illness decreases with age, with 2-3 illnesses per year by adulthood. The incidence of infection is primarily a function of exposure to the virus. Children in out-of-home daycare centers during the 1st yr of life have 50% more colds than children cared for only at home. The difference in the incidence of illness between these groups of children decreases as the length of time spent in daycare increases, although the incidence of illness remains higher in the daycare group through at least the 1st 3 yr of life. When they begin primary school, children who attended daycare have less frequent colds than those who did not. Mannose-binding lectin deficiency with impaired innate immunity may be associated with an increased incidence of colds in children.

**PATHOGENESIS**

Viruses that cause the common cold are spread by 3 mechanisms: direct hand contact (self-inoculation of one’s own nasal mucosa or conjunctiva after touching a contaminated person or object), inhalation of small-particle aerosols that are airborne from coughing, or deposition of large-particle aerosols that are expelled during a sneeze and land on nasal or conjunctival mucosa. Although the different common cold pathogens could be spread by any of these mechanisms, some routes of transmission appear to be more efficient than others for particular viruses. Studies of rhinoviruses and RSV indicate that direct contact is an efficient mechanism of transmission of these viruses, although transmission by large-particle aerosols can also occur. By contrast, influenza viruses and coronaviruses appear to be most efficiently spread by small-particle aerosols.

The respiratory viruses have evolved different mechanisms to avoid host defenses. Infections with rhinoviruses and adenoviruses result in the development of serotype-specific protective immunity. Repeated infections with these pathogens occur because there are a large number of distinct serotypes of each virus. Influenza viruses have the ability to change the antigens presented on the surface of the virus and thus behave as though there were multiple viral serotypes. The interaction of coronaviruses (see Chapter 264) with host immunity is not well defined, but it appears that multiple distinct strains of coronaviruses are capable of inducing at least short-term protective immunity. There are 4 types of parainfluenza viruses and 2 antigenic subgroups of RSV. In addition to antigenic diversity, many of these viruses are able to
reinfect the upper airway because mucosal immunoglobulin A induced by previous infection is short-lived, and the brief incubation period of these viruses allows the establishment of infection before immune memory responses. Although reinfection is not completely prevented by the adaptive host response to these viruses, the severity of illness is moderated by preexisting immunity.

Viral infection of the nasal epithelium can be associated with destruction of the epithelial lining, as with influenza viruses and adenoviruses, or there can be no apparent histologic damage, as with rhinoviruses and RSV. Regardless of the histopathologic findings, infection of the nasal epithelium is associated with an acute inflammatory response characterized by release of a variety of inflammatory cytokines and infiltration of the mucosa by inflammatory cells. This acute inflammatory response appears to be partially or largely responsible for many of the symptoms associated with the common cold. Viral shedding of most respiratory viruses peaks 3-5 days after inoculation, often coinciding with symptom onset; low levels of viral shedding may persist for up to 2 wk in the otherwise healthy host. Inflammation can obstruct the sinus ostia or eustachian tube, predisposing to bacterial sinusitis or otitis media.

The host immune system is responsible for most cold symptoms, rather than direct damage to the respiratory tract. Infected cells release cytokines, such as interleukin-8, that attract polymorphonuclear cells into the nasal submucosa and epithelium. Rhinoviruses also increase vascular permeability in the nasal submucosa, releasing albumin and bradykinin, which may contribute to symptoms.

**CLINICAL MANIFESTATIONS**

Symptoms of the common cold vary by age and virus. In infants, fever and nasal discharge may predominate. Fever is uncommon in older children and adults. The onset of common cold symptoms typically occurs 1-3 days after viral infection. The first symptom noted is often sore or scratchy throat, followed closely by nasal obstruction and rhinorrhea. The sore throat usually resolves quickly and, by the 2nd and 3rd day of illness, nasal symptoms predominate. Cough is associated with two-thirds of colds in children and usually begins after the onset of nasal symptoms. Cough may persist for an additional 1-2 wk after resolution of other symptoms. Influenza viruses, RSVs, human metapneumovirus, and adenoviruses are more likely than rhinoviruses or coronaviruses to be associated with fever and other constitutional symptoms. Other symptoms of a cold may include headache, hoarseness, irritability, difficulty sleeping, or decreased appetite. Vomiting and diarrhea are uncommon. The usual cold persists for approximately 1 wk, although 10% last for 2 wk.

The physical findings of the common cold are limited to the upper respiratory tract. Increased nasal secretion is usually obvious; a change in the color or consistency of the secretions is common during the course of the illness and does not indicate sinusitis or bacterial superinfection but may indicate accumulation of polymorphonuclear cells. Examination of the nasal cavity might reveal swollen, erythematous nasal turbinates, although this finding is nonspecific and of limited diagnostic value. Abnormal middle ear pressure is common during the course of a cold. Anterior cervical lymphadenopathy or conjunctival injection may also be noted on exam.

**DIAGNOSIS**

The most important task of the physician caring for a patient with a cold is to exclude other conditions that are potentially more serious or treatable. The differential diagnosis of the common cold includes noninfectious disorders as well as other upper respiratory tract infections (Table 379-2).

**LABORATORY FINDINGS**

Routine laboratory studies are not helpful for the diagnosis and management of the common cold. A nasal smear for eosinophils may be useful if allergic rhinitis is suspected (see Chapter 143). A predominance of polymorphonuclear cells in the nasal secretions is characteristic of uncomplicated colds and does not indicate bacterial superinfection. Self-limited radiographic abnormalities of the paranasal sinuses are common during an uncomplicated cold; imaging is not indicated for most children with simple rhinitis. The viral pathogens associated with the common cold can be detected by polymerase chain reaction, culture, antigen detection, or

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**Table 379-1** Pathogens Associated with the Common Cold

<table>
<thead>
<tr>
<th>ASSOCIATION</th>
<th>PATHOGEN</th>
<th>RELATIVE FREQUENCY*</th>
<th>OTHER COMMON SYMPTOMS AND SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents primarily associated with the common cold</td>
<td>Human rhinoviruses</td>
<td>Frequent</td>
<td>Wheezing/bronchiolitis</td>
</tr>
<tr>
<td></td>
<td>Coronaviruses</td>
<td>Occasional</td>
<td></td>
</tr>
<tr>
<td>Agents primarily associated with other clinical syndromes that also cause common cold symptoms</td>
<td>Respiratory syncytial viruses</td>
<td>Occasional</td>
<td>Bronchiolitis in children &lt;2 yr of age</td>
</tr>
<tr>
<td></td>
<td>Human metapneumovirus</td>
<td>Occasional</td>
<td>Pneumonia and bronchiolitis</td>
</tr>
<tr>
<td></td>
<td>Influenza viruses</td>
<td>Uncommon</td>
<td>Influenza, pneumonia, croup</td>
</tr>
<tr>
<td></td>
<td>Parainfluenza viruses</td>
<td>Uncommon</td>
<td>Croup, bronchiolitis</td>
</tr>
<tr>
<td></td>
<td>Adenoviruses</td>
<td>Uncommon</td>
<td>Pharyngoconjunctival fever (palpebral conjunctivitis, watery eye discharge, pharyngeal erythema)</td>
</tr>
<tr>
<td></td>
<td>Enteroviruses</td>
<td>Uncommon</td>
<td>Herpangina (fever and ulcerated papules on posterior oropharynx)</td>
</tr>
<tr>
<td></td>
<td>Coxsackievirus A</td>
<td>Uncommon</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td></td>
<td>Other nonpolio enteroviruses</td>
<td>Uncommon</td>
<td></td>
</tr>
</tbody>
</table>

*Relative frequency of colds caused by the agent.

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**Table 379-2** Conditions That Can Mimic the Common Cold

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DIFFERENTIATING FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>Prominent itching and sneezing, nasal eosinophils</td>
</tr>
<tr>
<td>Vasomotor rhinitis</td>
<td>May be triggered by irritants, weather changes, spicy foods, etc.</td>
</tr>
<tr>
<td>Rhinitis medicamentosa</td>
<td>History of nasal decongestant use</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Unilateral, foul-smelling secretions</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Bloody nasal secretions</td>
</tr>
<tr>
<td>Streptococcosis</td>
<td>Presence of fever, headache or facial pain, or peri orbital edema or persistence of rhinorrhea or cough for longer than 14 days</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Mucopurulent nasal discharge that excoriates the nares</td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td>Persistent rhinorrhea with onset in the 1st 3 mo of life</td>
</tr>
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</table>

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</tbody>
</table>
serologic methods. These studies are generally not indicated in patients with colds because a specific etiologic diagnosis is useful only when treatment with an antiviral agent is contemplated, such as for influenza viruses. Bacterial cultures or antigen detection are useful only when group A streptococcus (see Chapter 183) or Bordetella pertussis (see Chapter 197) is suspected. The isolation of other bacterial pathogens from nasopharyngeal specimens is not an indication of bacterial nasal infection and is not a specific predictor of the etiologic agent in sinusitis.

**TREATMENT**

The management of the common cold consists primarily of supportive care and anticipatory guidance as recommended by American Academy of Pediatrics and United Kingdom National Institute for Health and Clinical Excellence guidelines.

**Antiviral Treatment**

Specific antiviral therapy is not available for rhinovirus infections. Ribavirin, which is approved for treatment of severe RSV infections, has no role in the treatment of the common cold. The neuraminidase inhibitors oseltamivir and zanamivir have a modest effect on the duration of symptoms associated with influenza viral infections in children. Oseltamivir also reduces the frequency of influenza-associated otitis media. The difficulty of distinguishing influenza from other common cold pathogens and the necessity that therapy be started early in the illness (within 48 hr of onset of symptoms) to be beneficial are practical limitations to the use of these agents for mild upper respiratory tract infections. Antibacterial therapy is of no benefit in the treatment of the common cold and should be avoided to minimize possible adverse effects and the development of antibiotic resistance.

**Supportive Care and Symptomatic Treatment**

Supportive interventions are frequently recommended by providers. Maintaining adequate oral hydration may help to thin secretions and soothe respiratory mucosa. The common home remedy of ingesting warm fluids may soothe mucosa, increase nasal mucous flow, or loosen respiratory secretions. Topical nasal saline may temporarily remove irritation associated with postnasal drip. Cough in these patients is cough in some patients appears to be from upper respiratory tract infections because of the risk of Reye syndrome in children with influenza (see Chapter 361). *Nonsteroidal antiinflammatory drugs* are somewhat effective in relieving discomfort caused by a cold, but there is no clear evidence of their effect on respiratory symptoms. The balance of harm and benefits must be considered when using nonsteroidal antiinflammatory drugs for colds.

**Fever**

Fever is not usually associated with an uncomplicated common cold, and antipyretic treatment is generally not indicated.

**Nasal Obstruction**

Either topical or oral adrenergic agents may be used as nasal decongestants in older children and adults. Effective topical adrenergic agents such as xylometazoline, oxymetazoline, or phenylephrine are available as either intranasal drops or nasal sprays. Reduced-strength formulations of these medications are available for use in younger children, although they are not recommended for use in children younger than 6 yr old. Systemic absorption of the imidazolines (oxymetazoline, xylometazoline) has very rarely been associated with bradycardia, hypotension, and coma. Prolonged use of the topical adrenergic agents should be avoided to prevent the development of *rhinitis medicamentosa*, an apparent rebound effect that causes the sensation of nasal obstruction when the drug is discontinued. The oral adrenergic agents are less effective than the topical preparations and are occasionally associated with systemic effects such as central nervous system stimulation, hypertension, and palpitations. Aromatic vapors (such as menthol) for external rub may improve perception of nasal patency, but do not affect spirometry. Saline nose drops (wash, irrigation) can improve nasal symptoms and may be used in all age groups.

**Rhinorrhea**

The first-generation antihistamines may reduce rhinorrhea by 25-30%. The effect of the antihistamines on rhinorrhea appears to be related to the anticholinergic rather than the antihistaminic properties of these drugs, and therefore the second-generation or “nonsedating” antihistamines have no effect on common cold symptoms. The major adverse effects associated with the use of the antihistamines are sedation or paradoxical hyperactivity. Overdose may be associated with respiratory depression or hallucinations. Rhinorrhea may also be treated with ipratropium bromide, a topical anticholinergic agent. This drug produces an effect comparable to the antihistamines but is not associated with sedation. The most common side effects of ipratropium are nasal irritation and bleeding.

**Sore Throat**

The sore throat associated with colds is generally not severe, but treatment with mild analgesics is occasionally indicated, particularly if there is associated myalgia or headache. The use of acetaminophen during rhinovirus infection is associated with suppression of neutralizing antibody responses, but this observation has no apparent clinical significance. Aspirin should not be given to children with respiratory infections because of the risk of Reye syndrome in children with influenza (see Chapter 361). *Nonsteroidal antiinflammatory drugs* are somewhat effective in relieving discomfort caused by a cold, but there is no clear evidence of their effect on respiratory symptoms. The balance of harm and benefits must be considered when using nonsteroidal antiinflammatory drugs for colds.

**Cough**

Cough suppression is generally not necessary in patients with colds. Cough in some patients appears to be from upper respiratory tract irritation associated with postnasal drip. Cough in these patients is most prominent during the time of greatest nasal symptoms, and treatment with a first-generation antihistamine may be helpful. Cough lozenges or hard candy may be temporarily effective and are unlikely to be harmful in children for whom they do not pose risk of aspiration (older than age 6 yr). *Honey* (5-10 mL in children ≥1 year old) has a modest effect on relieving nocturnal cough and is unlikely to be harmful in children older than 1 yr of age. Honey should be avoided in children younger than 1 yr of age because of the risk for botulism (see Chapter 210).
In some patients, cough may be a result of virus-induced reactive airways disease. These patients can have cough that persists for days to weeks after the acute illness and might benefit from bronchodilator or other therapy. Codeine or dextromethorphan hydrobromide has no effect on cough from colds and has potential enhanced toxicity. Expectorants such as guaifenesin are not effective antitussive agents. The combination of camphor, menthol, and eucalyptus oils may relieve nocturnal cough, but studies of their effectiveness are limited.

**Ineffective Treatments**

Vitamin C, guaifenesin, and inhalation of warm, humidified air are no more effective than placebo for the treatment of cold symptoms.

Echinacea is a popular herbal treatment for the common cold. Although echinacea extracts have biologic effects, echinacea is not effective as a common cold treatment. The lack of standardization of commercial products containing echinacea also presents a formidable obstacle to the rational evaluation or use of this therapy.

There is no evidence that the common cold or persistent acute purulent rhinitis of less than 10 days in duration benefits from antibiotics. In fact, there is evidence that antibiotics cause significant adverse effects when given for acute purulent rhinitis.

**COMPLICATIONS**

The most common complication of a cold is acute otitis media (AOM; see Chapter 640), which may be indicated by new-onset fever and earache after the first few days of cold symptoms. AOM is reported in 5-30% of children who have a cold, with the higher incidence occurring in young infants and in children cared for in a group daycare setting. Symptomatic treatment has no effect on the development of AOM, but treatment with oseltamivir might reduce the incidence of AOM in patients with influenza.

Sinusitis is another complication of the common cold (see Chapter 380). Self-limited sinus inflammation is a part of the pathophysiology of the common cold, but 0.5-2% of viral upper respiratory tract infections in adults, and 5-13% in children, are complicated by acute bacterial sinusitis. The differentiation of common cold symptoms from bacterial sinusitis may be difficult. The diagnosis of bacterial sinusitis should be considered if rhinorrhea or daytime cough persists without improvement for at least 10-14 days, if symptoms worsen over time, or if signs of more severe sinus involvement such as fever, facial pain, or facial swelling develop. There is no evidence that symptomatic treatment of the common cold alters the frequency of development of bacterial sinusitis. Bacterial pneumonia is an uncommon complication of the common cold.

Exacerbation of asthma is a relatively uncommon but potentially serious complication of colds. The majority of asthma exacerbations in children are associated with the common cold. There is no evidence that treatment of common cold symptoms prevents this complication; however, studies are underway in patients with underlying asthma to determine effectiveness of preventive or acute treatment at the onset of upper respiratory tract infection symptoms.

Although not a complication, another important consequence of the common cold is the inappropriate use of antibiotics for these illnesses and the associated contribution to the problem of increasing antibiotic resistance of pathogenic respiratory bacteria, as well as adverse effects from antibiotics.

**PREVENTION**

Chemoprophylaxis or immunoprophylaxis is generally not available for the common cold. Immunization or chemoprophylaxis against influenza can prevent colds caused by this pathogen; influenza is responsible for only a small proportion of all colds. Palivizumab is recommended to prevent RSV lower respiratory infection in high-risk infants but does not prevent upper respiratory infections from this virus. Vitamin C, garlic, or echinacea do not prevent the common cold. Vitamin D deficiency is associated with increased risk of viral respiratory tract infection in some studies, nonetheless, vitamin D prophylaxis does not reduce incidence or severity of the common cold in adults; studies in children are lacking. Zinc sulfate taken for a minimum of 5 mo may reduce the rate of cold development. However, because of duration of use and adverse effects of bad taste and nausea, this is not a recommended prevention modality in children.

Hand-to-hand transmission of rhinoviruses followed by self-inoculation may be prevented by frequent hand washing and avoiding touching one’s mouth, nose, and eyes. Some studies report the use of alcohol-based hand sanitizers and virucidal hand treatments were associated with decreased transmission. In the experimental setting, virucidal disinfectants or virucidal-impregnated tissues also reduce transmission of cold viruses; under natural conditions none of these interventions prevents common colds.

Bibliography is available at Expert Consult.
### Bibliography


Sinusitis is a common illness of childhood and adolescence. There are 2 types of acute sinusitis: viral and bacterial, with significant acute and chronic morbidity as well as the potential for serious complications. The common cold produces a viral, self-limited rhinosinusitis (see Chapter 379). Approximately 0.5-2% of viral upper respiratory tract infections in children and adolescents are complicated by acute symptomatic bacterial sinusitis. Some children with underlying predisposing conditions have chronic sinus disease that does not appear to be infectious. The means for appropriate diagnosis and optimal treatment of sinusitis remain controversial.

Typically the ethmoidal and maxillary sinuses are present at birth, but only the ethmoidal sinuses are pneumatized. The maxillary sinuses are not pneumatized until 4 yr of age. The sphenoidal sinuses are present by 5 yr of age, whereas the frontal sinuses begin development at age 7-8 yr and are not completely developed until adolescence. The ostia draining the sinuses are narrow (1-3 mm) and drain into the ostiomeatal complex in the middle meatus. The paranasal sinuses are normally sterile, maintained by the mucociliary clearance system.

ETIOLOGY
The bacterial pathogens causing acute bacterial sinusitis in children and adolescents include Streptococcus pneumoniae (~30%; see Chapter 182), nontypeable Haemophilus influenzae (~20%; see Chapter 194), and Moraxella catarrhalis (~20%; see Chapter 196). Approximately 50% of H. influenzae and 100% of M. catarrhalis are β-lactamase positive. Approximately 25% of S. pneumoniae may be penicillin resistant. Staphylococcus aureus, other streptococci, and anaerobes are uncommon causes of acute bacterial sinusitis in children. Although S. aureus (see Chapter 181.1) is an uncommon pathogen for acute sinusitis in children, the increasing prevalence of methicillin-resistant S. aureus is a significant concern. H. influenzae, α- and β-hemolytic streptococci, M. catarrhalis, S. pneumoniae, and coagulase-negative staphylococci are commonly recovered from children with chronic sinus disease.

EPIDEMIOLOGY
Acute bacterial sinusitis can occur at any age. Predisposing conditions include viral upper respiratory tract infections (associated with out-of-home daycare or a school-age sibling), allergic rhinitis, and cigarette smoke exposure. Children with immune deficiencies particularly of antibody production (immunoglobulin IgG, IgG subclasses, IgA; see Chapter 124), cystic fibrosis (see Chapter 403), ciliary dysfunction (see Chapter 404), abnormalities of phagocyte function,
gastroesophageal reflux, anatomic defects (cleft palate), nasal polyps, cocaine abuse, and nasal foreign bodies (including nasogastric tubes) can develop chronic or recurrent sinus disease. Immunosuppression for bone marrow transplantation or malignancy with profound neutropenia and lymphopenia predisposes to severe fungal (aspergillus, mucor) sinusitis, often with intracranial extension. Patients with nasotracheal intubation or nasogastric tubes may have obstruction of the sinus ostia and develop sinusitis with the multiple-drug resistant organisms of the intensive care unit.

Acute sinusitis is defined by duration of <30 days; subacute by duration of 1-3 mo; and chronic by duration of longer than 3 mo.

**PATHOGENESIS**

Acute bacterial sinusitis typically follows a viral upper respiratory tract infection. Initially, the viral infection produces a viral rhinosinusitis; MRI evaluation of the paranasal sinuses demonstrates abnormalities (mucosal thickening, edema, inflammation) of the paranasal sinuses in 68% of healthy children in the normal course of the common cold. Nose blowing has been demonstrated to generate sufficient force to propel nasal secretions into the sinus cavities. Bacteria from the nasopharynx that enter the sinuses are normally cleared readily, but during viral rhinosinusitis, inflammation and edema can block sinus drainage and impair mucociliary clearance of bacteria. The growth conditions are favorable, and high titers of bacteria are produced.

**CLINICAL MANIFESTATIONS**

Children and adolescents with sinusitis can present with nonspecific complaints, including nasal congestion, purulent nasal discharge (unilateral or bilateral), fever, and cough. Less common symptoms include bad breath (halitosis), a decreased sense of smell (hyposmia), and periorbital edema. Complaints of headache and facial pain are rare in children. Additional symptoms include maxillary tooth discomfort and pain or pressure exacerbated by bending forward. Physical examination might reveal erythema and swelling of the nasal mucosa with purulent nasal discharge. Sinus tenderness may be detectable in adolescents and adults. Transillumination reveals an opaque sinus that transmits light poorly.

Differentiating bacterial sinusitis from a cold may be difficult, but certain patterns suggestive of sinusitis have been identified. These include persistence of nasal congestion, rhinorrhea (of any quality) and daytime cough ≥210 days without improvement; severe symptoms of temperature ≥39°C (102°F) with purulent nasal discharge for 3 days or longer; and worsening symptoms either by recurrence of symptoms after an initial improvement or new symptoms of fever, nasal discharge and daytime cough.

**DIAGNOSIS**

The clinical diagnosis of acute bacterial sinusitis is based on history. Persistent symptoms of upper respiratory tract infection, including nasal discharge and cough, for longer than 10 days without improvement, or severe respiratory symptoms, including temperature of at least 39°C (102°F) and purulent nasal discharge for 3-4 consecutive days, suggest a complicating acute bacterial sinusitis. Bacteria are recovered from maxillary sinus aspirates in 70% of children with such persistent or severe symptoms studied. Children with chronic sinusitis have a history of persistent respiratory symptoms, including cough, nasal discharge, or nasal congestion, lasting longer than 90 days.

*Sinus aspirate culture* is the only accurate method of diagnosis but is not practical for routine use for immunocompetent patients. It may be a necessary procedure for immunosuppressed patients with suspected fungal sinusitis. In adults, *rigid nasal endoscopy* is a less-invasive method for obtaining culture material from the sinus but detects a great excess of positive cultures compared to aspirates. Findings on radiographic studies (sinus plain films, CT scans) including opacification, mucosal thickening, or presence of an air–fluid level are not diagnostic (Fig. 380-1) and are not recommended in otherwise healthy children. Such findings can confirm the presence of sinus inflammation but cannot be used to differentiate among viral, bacterial, or allergic causes of inflammation.

Given the nonspecific clinical picture, differential diagnostic considerations include viral upper respiratory tract infection, allergic rhinitis, nonallergic rhinitis, and nasal foreign body. Viral upper respiratory tract infections are characterized by clear and usually nonpurulent nasal discharge, cough, and initial fever; symptoms do not usually persist beyond 10-14 days, although a few children (10%) have persistent symptoms even at 14 days. Allergic rhinitis can be seasonal; evaluation of nasal secretions should reveal significant eosinophilia.

**TREATMENT**

It is unclear whether antimicrobial treatment of clinically diagnosed acute bacterial sinusitis offers any substantial benefit. A randomized, placebo-controlled trial comparing 14-day treatment of children with clinically diagnosed sinusitis with amoxicillin, amoxicillin-clavulanate, or placebo found that antimicrobial therapy did not affect resolution of symptoms, duration of symptoms, or days missed from school. A similar study in adults demonstrated improved symptoms at day 7 but not day 10 of treatment. Guidelines from the American Academy of Pediatrics recommend antimicrobial treatment for acute bacterial sinusitis with severe onset or a worsening course to promote resolution of symptoms and prevent suppurative complications, although 50-60% of children with acute bacterial sinusitis recover without antimicrobial therapy.

Initial therapy with amoxicillin (45 mg/kg/day divided bid) is adequate for the majority of children with uncomplicated mild to moderate severity acute bacterial sinusitis. Alternative treatments for the penicillin-allergic patient include cefdinir, cefuroxime axetil, cefpodoxime, or cefixime. In older children, levofloxacin is an alternative antibiotic. Azithromycin and trimethoprim-sulfamethoxazole are no longer indicated because of a high prevalence of antibiotic resistance. For children with risk factors (antibiotic treatment in the preceding 1-3 mo, daycare attendance, or age younger than 2 yr) for the presence of resistant bacterial species, and for children who fail to respond to initial therapy with amoxicillin within 72 hr, or with severe sinusitis, treatment with high-dose amoxicillin-clavulanate (80-90 mg/kg/day of amoxicillin) should be initiated. Ceftriaxone (50 mg/kg, IV or IM) may be given to children who are vomiting or who are at risk for poor compliance; it should be followed by a course of oral antibiotics. Failure to respond to these regimens necessitates referral to an otolaryngologist for further evaluation because maxillary sinus aspiration for culture and susceptibility testing may be necessary. The appropriate duration of therapy for sinusitis has yet to be determined; individualization of therapy is a reasonable approach, with treatment recommended for a minimum of 10 days or 7 days after resolution of symptoms (see Fig. 380-1).

Frontal sinusitis can rapidly progress to serious intracranial complications and necessitates initiation of parenteral ceftriaxone until substantial clinical improvement is achieved (Figs. 380-2 and 380-3). Treatment is then completed with oral antibiotic therapy.

The use of decongestants, antihistamines, mucolytics, and intranasal corticosteroids has not been adequately studied in children and is not recommended for the treatment of acute uncomplicated bacterial sinusitis. Likewise, saline nasal washes or nasal sprays can help to liquefy secretions and act as a mild vasoconstrictor, but the effects have not been systematically evaluated in children.

**COMPLICATIONS**

Because of the close proximity of the paranasal sinuses to the brain and eyes, serious orbital and/or intracranial complications can result from acute bacterial sinusitis and progress rapidly. Orbital complications, including *periOrbital cellulitis* and *orbital cellulitis* (see Chapter 634) are most often secondary to acute bacterial ethmoiditis. Infection can spread directly through the lamina papyracea, the thin bone that forms the lateral wall of the ethmoidal sinus. PeriOrbital cellulitis produces erythema and swelling of the tissues surrounding the globe, whereas orbital cellulitis involves the intraorbital structures and produces proptosis, chemosis, decreased visual acuity, double vision and impaired extraocular movements, and eye pain (Fig. 380-4). Evaluation should include CT scan of the orbits and sinuses with ophthalmology and otolaryngology consultations. Treatment with intravenous antibiotics...
Intracranial complications can include epidural abscess, meningitis, cavernous sinus thrombosis, subdural empyema, and brain abscess (see Chapter 604). Children with altered mental status, nuchal rigidity, severe headache, focal neurologic findings, or signs of increased intracranial pressure (headache, vomiting) require immediate CT scan of the brain, orbits, and sinuses to evaluate for the presence of intracranial complications of acute bacterial sinusitis. Black children and males are at increased risk, but there is no evidence of increased risk due to socioeconomic status. Treatment with broad-spectrum intravenous antibiotics (usually cefotaxime or ceftriaxone combined with vancomycin) should be initiated immediately, pending culture and susceptibility results. In 50% the abscess is a polymicrobial infection. Abscesses can require surgical drainage. Other complications include osteomyelitis of the frontal bone (Pott puffy tumor), which is characterized by edema and swelling of the forehead (see Fig. 380-3), and mucoceles, which are chronic inflammatory lesions commonly located in the frontal sinuses that can expand, causing displacement of the eye with resultant diplopia. Surgical drainage is usually required.

PREVENTION
Prevention is best accomplished by frequent handwashing and avoiding persons with colds. Because acute bacterial sinusitis can complicate...
influenza infection, prevention of influenza infection by yearly influenza vaccine will prevent some cases of complicating sinusitis. Immunization or chemoprophylaxis against influenza with oseltamivir or zanamivir may be useful for prevention of colds caused by this pathogen and the associated complications; influenza is responsible for only a small proportion of all colds.

Bibliography is available at Expert Consult.

Figure 380-3 Axial plane contrast-enhanced CT scan of an 11 yr old obtunded girl with a subfrontal lobe abscess secondary to frontal sinusitis. The CT scan demonstrates an elliptiform ring-enhancing fluid-filled cavity adjacent to the frontal lobe with contralateral shift of the midline. (From Parikh SR, Brown SM: Image-guided frontal sinus surgery in children, Operative Tech Otolaryngol Head Neck Surg 15:37–41, 2004.)

Figure 380-4 Orbital complications of acute sinusitis. A, An 11 mo old infant with a swollen left eye and limited ocular movement. B, Axial CT shows opacification of sinuses and an inflammatory mass with an air-fluid level displacing the medial rectus laterally. (From Cooper, ML, Slovis T. The sinuses. In Slovis T, editor: Caffey's pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 43-7, p. 573.)
Bibliography
Pharyngitis refers to inflammation of the pharynx, including erythema, edema, exudates, or an enanthem (ulcers, vesicles). Pharyngeal inflammation can be related to environmental exposures, such as tobacco smoke, air pollutants, and allergens; from contact with caustic substances, hot food, and liquids; and from infectious agents. The pharynx and mouth can be involved in various inflammatory conditions such as the periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome, Kawasaki disease, inflammatory bowel disease, Stevens-Johnson syndrome, and systemic lupus erythematous. Noninfectious etiologies are typically evident from history and physical exam, but it can be more challenging to distinguish from among the numerous infectious causes of acute pharyngitis.

Acute infections of the upper respiratory tract account for a substantial number of visits to pediatricians and many feature sore throat as a symptom or evidence of pharyngitis on physical examination. The usual clinical task is to distinguish important, potentially serious, and treatable causes of acute pharyngitis from those that are self-limited and require no specific treatment or follow-up. Specifically, identifying patients who have *group A streptococcus* (GAS; *Streptococcus pyogenes*; see Chapter 183) pharyngitis and treating them with antibiotics forms the core of the management paradigm.

**INFECTIOUS ETIOLOGIES**

See Table 381-1.

**Viruses**

In North America and most industrialized countries GAS is the most important bacterial cause of acute pharyngitis, but viruses predominate as acute infectious causes of pharyngitis. Viral upper respiratory tract infections are typically spread by contact with oral or respiratory secretions and occur most commonly in fall, winter, and spring, that is, the “respiratory season.” Important viruses that cause pharyngitis include influenza (see Chapter 258), parainfluenza (see Chapter 259), adenoviruses (see Chapter 262), coronaviruses (see Chapter 264), enteroviruses (see Chapter 250), rhinoviruses (see Chapter 263), respiratory
syncytial virus (see Chapter 260), cytomegalovirus (see Chapter 255), Epstein-Barr virus (see Chapter 254), herpes simplex virus (see Chapter 252), and human metapneumovirus (see Chapter 261). Most viral pharyngitis, except mononucleosis, is mild. Common nonspecific symptoms such as rhinorrhea and cough develop gradually before they become prominent. However, specific findings are sometimes helpful in identifying the infectious viral agent.

**Gingivostomatitis and ulcerating vesicles** throughout the anterior pharynx and on the lips are seen in primary oral herpetic virus infection. High fever and difficulty taking oral fluids are common. This infection can last for 14 days.

Discrete papulovesicular lesions or ulcerations in the posterior oropharynx, severe throat pain, and fever are characteristic of herpangina, caused by various enteroviruses. In hand-foot-mouth disease there are vesicles or ulcers throughout the oropharynx, vesicles on the palms and soles, and sometimes on the trunk and extremities; Coxsackie A16 is the most common agent, but Enterovirus 71 and Coxsackie A6 can also cause this syndrome. Enteroviral infections are most common in the summer.

Various adenoviruses cause pharyngitis. When there is concurrent conjunctivitis the syndrome is called *pharyngoconjunctival fever*. The pharyngitis tends to resolve within 7 days but conjunctivitis may persist for up to 14 days. Pharyngoconjunctival fever can be epidemic or sporadic; outbreaks have been associated with exposure in swimming pools.

Intense, diffuse pharyngeal erythema and Koplik spots, the pathognomonic enanthem, occur in advance of the characteristic rash of measles. Splenomegaly or hepatomegaly may be the clue to Epstein-Barr virus infectious mononucleosis in an adolescent with exudative pharyngitis, gastrointestinal signs and symptoms should not be attributed to GAS. Ear pain is a frequent complaint but the tympanic membranes are usually normal. Diarrhea, cough, coryza, ulcerations, and a pseudomembrane (as in diphtheria) may be present. *M. pneumoniae* and *C. pneumoniae* cause pharyngitis, but other upper and lower respiratory infections are more important and more readily recognized. Development of a severe or persistent cough subsequent to pharyngitis may be the clue to infection with one of these organisms.

**Group A Streptococcus**

Streptococcal pharyngitis is relatively uncommon before 2-3 yr of age, is quite common among children 5-15 yr old, and declines in frequency in late adolescence and adulthood. Illness occurs throughout the year but is most prevalent in winter and spring. It is readily spread among siblings and schoolmates. GAS causes 15-30% of pharyngitis in school-age children.

Colonization of the pharynx by GAS can result in either asymptomatic carriage or acute infection. After an incubation period of 2-5 days, pharyngeal infection with GAS classically presents as rapid onset of significant sore throat and fever. The pharynx is red, the tonsils are enlarged and often covered with a white, grayish, or yellow exudate that may be blood-tinged. There may be petechiae or “doughnut” lesions on the soft palate and posterior pharynx and the uvula may be red and swollen. The surface of the tongue can resemble a strawberry when the papillae are inflamed and prominent (“strawberry tongue”). Initially, the tongue is often coated white, and with the swollen papillae it is called a “white strawberry tongue.” When the white coating is gone after a few days, the tongue is often quite red, and is called a “red strawberry tongue.” Enlarged and tender anterior cervical lymph nodes are frequently present. Headache, abdominal pain, and vomiting are frequently associated with the infection, but in the absence of clinical pharyngitis, gastrointestinal signs and symptoms should not be attributed to GAS. Ear pain is a frequent complaint but the tympanic membranes are usually normal. Diarrhea, cough, coryza, ulcerations, croup/laryngitis/hoarseness, and conjunctivitis are not associated with GAS pharyngitis and increase the likelihood of a viral etiology.

Patients infected with GAS that produce streptococcal pyrogenic exotoxin A, B, or C may demonstrate the fine red, papular (“sandpaper”) rash of scarlet fever. It begins on the face and then becomes generalized. The cheeks are red and the area around the mouth is more pale, giving the appearance of circulatory pallor. The rash blanches with pressure and it may be more intense in skin creases, especially in the antecubital fossae, axillae, and inguinal creases (Pastia’s lines or Pastia’s sign). Pastia’s lines are sometimes petechial or slightly hemorrhagic.

**F. necrophorum** has been suggested to be a fairly common cause of pharyngitis in older adolescents and adults (15-30 yr old). Prevalence in studies has varied from 10-48% of patients with non-GABHS pharyngitis, but large surveillance studies have not been performed. *F. necrophorum* pharyngitis is associated with development of *Lemierre syndrome*, internal jugular vein septic thrombophlebitis. Approximately 80% of cases of Lemierre syndrome are caused by this bacterium. Patients present initially with fever, sore throat, exudative pharyngitis, and/or peritonsillar abscess. The symptoms may persist, neck pain and swelling develop, and the patient appears toxic. Septic embolus may ensue along with metastatic complications from septic emboli that can involve the lungs, bones and joints, central nervous system, abdominal organs, and soft tissues. The case fatality rate is 4-9%.

Gonococcal pharyngeal infections are usually asymptomatic but can cause acute pharyngitis with fever and cervical lymphadenitis. Young children with proven gonococcal disease should be evaluated for sexual abuse.

Diphtheria is extremely rare in most developed countries thanks to extensive immunization with diphteria toxoid. However, it remains endemic in many areas of the world, including the former Soviet bloc countries, Africa, Asia, the Middle East, and Latin America. It can be considered in patients with recent travel to or from these areas and in unimmunized patients. Key physical findings are bull neck (extreme neck swelling) and a gray pharyngeal pseudomembrane that can cause respiratory obstruction.

Ingestion of water, milk, or undercooked meat contaminated by *F. tularensis* can lead to oropharyngeal tularemia. Severe throat pain, tonsillitis, cervical adenitis, oral ulcerations, and a pseudomembrane (as in diphtheria) may be present. *M. pneumoniae* and *C. pneumoniae* cause pharyngitis, but other upper and lower respiratory infections are more important and more readily recognized. Development of a severe or persistent cough subsequent to pharyngitis may be the clue to infection with one of these organisms.
Capillary fragility can cause petechiae distal to a tourniquet or constric-
tion from clothing, a positive tourniquet test or Rumpel-Leeds phe-
omenon. Erythema fades in a few days and when the rash resolves it
typically peels like a mild sunburn. Sometimes there is sheet-like des-
quamation around the free margins of the finger nails. Streptococcal
pyrogenic exotoxin A, encoded by the gene spe A, is the exotoxin most
commonly associated with scarlet fever.

The M protein is an important GAS virulence factor that facilitates
resistance to phagocytosis. The M protein is encoded by the emm gene
determines the M type (or emm type). Molecular methods have
identified more than 200 emm genes (emm types). The M protein is
immunogenic; an individual can experience multiple episodes of GAS
pharyngitis in a lifetime because natural immunity is M type-specific.
Numerous GAS M types can circulate in a community simultaneously
and they enter and leave communities unpredictably and for unknown
reasons.

**DIAGNOSIS**

The clinical presentations of streptococcal and viral pharyngitis often
overlap. In particular, the pharyngitis of mononucleosis can be difficult
to distinguish from GAS pharyngitis. Physicians relying solely on clinici-
al judgment often overestimate the likelihood of a streptococcal etiol-
ogy. Various clinical scoring systems have been described to assist in
identifying patients who are likely to have GAS pharyngitis. Criteria
developed for adults and modified for children by McIsaac give 1
point for each of the following criteria: history of temperature
≥38°C (100.4°F); absence of cough; tender anterior cervical adenopathy;
tonsillar swelling or exudates; and age 3-14 yr. It subtracts a point for age
≥45 yr. At best, a McIsaac score ≥4 is associated with a positive labora-
tory test for GAS in less than 70% of children with pharyngitis (Table
381-2), so it, too, overestimates the likelihood of GAS. Consequently,
laboratory testing is essential for accurate diagnosis. Clinical findings
and/or scoring systems can best be used to assist the clinician in iden-
tifying patients in need of testing. Streptococcal antibody tests are not
useful in assessing patients with acute pharyngitis.

Throat culture and rapid antigen-detection tests (RADTs) are the
diagnostic tests for GAS available in routine clinical care. Throat
culture remains the “gold standard” for diagnosing streptococcal pharyn-
gitis. There are both false-negative cultures as a consequence of
sampling errors or prior antibiotic treatment and false-positive cul-
tures as a consequence of misidentification of other bacteria as GAS.
Some laboratories prefer nucleic acid testing that is specific for GAS
and determines the M type (or emm type). Molecular methods have
identified more than 200 emm genes (emm types). The M protein is
immunogenic; an individual can experience multiple episodes of GAS
pharyngitis in a lifetime because natural immunity is M type-specific.
Numerous GAS M types can circulate in a community simultaneously
and they enter and leave communities unpredictably and for unknown
reasons.

**TREATMENT**

Specific therapy is unavailable for most viral pharyngitis. However,
nonspecific, symptomatic therapy can be an important part of the
overall treatment plan. An oral antipyretic/analgesic agent (acetamino-
phen or ibuprofen) can relieve fever and sore throat pain. Anesthetic
sprays and lozenges (often containing benzocaine, phenol, or menthol)
can provide local relief in children who are developmentally appropri-
ate to use them. Systemic corticosteroids are sometimes used in
children who have evidence of upper airway compromise due to
mononucleosis. Although corticosteroids are used fairly commonly in
adults with pharyngitis, large scale studies capable of providing safety
and efficacy data are lacking in children. Corticosteroids cannot be
recommended for treatment of most pediatric pharyngitis.

Antibiotic therapy of bacterial pharyngitis depends on the organism
identified. On the basis of in vitro susceptibility data, oral penicillin is
often suggested for patients with group C streptococcal isolates and
oral erythromycin is recommended for patients with *A. haemolyticum*,
but the clinical benefit of such treatment is uncertain.

Most untreated episodes of GAS pharyngitis resolve uneventful-
ly within 5 days, but early antibiotic therapy hastens clinical recovery by
12-24 hr. The primary benefit and intent of antibiotic treatment is the
prevention of acute rheumatic fever (ARF); it is highly effective when
started within 9 days of onset of illness. Antibiotic therapy does not
prevent acute poststreptococcal glomerulonephritis (APSGN). Anti-
biotic therapy should not be delayed for children with symptomatic
pharyngitis and a positive GAS RADT or throat culture. Presumptive
antibiotic treatment can be started when there is a clinical diagnosis of
scarlet fever, a symptomatic child has a household contact with

<table>
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<th>Table 381-2</th>
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<td><strong>SCORE</strong></td>
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<tr>
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<td>GAS prevalence</td>
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*One point is given for each of the following criteria: history of temperature ≥38°C (100.4°F); absence of cough; tender anterior cervical adenopathy; tonsillar swelling or exudates; and age 3-14 yr. Note that the Centor score lacks only the age criterion. Positive predictive value refers to the proportion of patients with documented GAS by rapid antigen-detection test and/or throat culture.*
Table 381-3  Recommended Treatment for Acute Streptococcal Pharyngitis

**MOST PATIENTS**

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<th>Duration</th>
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<tr>
<td>Penicillin V</td>
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<td>Oral</td>
<td>10 days</td>
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<tr>
<td>Benzathine penicillin G</td>
<td>600,000 units</td>
<td>IM</td>
<td>Once</td>
</tr>
<tr>
<td>Benzathine penicillin G + procaine penicillin G</td>
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**PENICillin-ALLERGIC PATIENTS**

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<th>Oral Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins*</td>
<td>Varies with agent chosen</td>
<td>10 days</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>260 mg/day divided in 3 doses bid</td>
<td>10 days</td>
</tr>
<tr>
<td>Ethylsuccinate</td>
<td>20-40 mg/kg/day up to 1000 mg/day bid</td>
<td>10 days</td>
</tr>
<tr>
<td>Estolate</td>
<td>40 mg/kg/day up to 1000 mg/day bid</td>
<td>10 days</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg/day up to 1000 mg/day bid</td>
<td>10 days</td>
</tr>
<tr>
<td>Azithromycin†</td>
<td>27 mg/kg for 5 days qd</td>
<td>5 days</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>20 mg/kg/day up to 1.8 g/day tid</td>
<td>10 days</td>
</tr>
</tbody>
</table>

*First-generation cephalosporins are preferred; dosage and frequency vary among agents. Do not use in patients with history of immediate (anaphylactic) hypersensitivity to penicillin or other β-lactam antibiotics.

†Maximum dose is 500 mg the 1st day, 250 mg subsequent days.

Documented streptococcal pharyngitis, or a history of ARF in the patient or a family member, but a diagnostic test should be performed to confirm the presence of GAS.

A variety of antimicrobial agents are effective for GAS pharyngitis (Table 381-3). Group A streptococci are universally susceptible to penicillin and all other β-lactam antibiotics. Penicillin is inexpensive, has a narrow spectrum of activity, and few adverse effects. Amoxicillin is preferred for children because of taste, availability as chewable tablets and liquid, and convenience of once-daily dosing. The duration of oral penicillin and amoxicillin therapy is 10 days. A single intramuscular dose of benzathine penicillin or a benzathine-procaine penicillin G combination is effective and ensures compliance. Follow-up testing for GAS is unnecessary after completion of therapy and is not recommended unless symptoms recur.

Patients allergic to penicillin can be treated with a 10-day course of a narrow-spectrum (first-generation) cephalosporin (cephalexin or cefadroxil) if the previous reaction to penicillin was not an immediate, type I hypersensitivity reaction. Most often, penicillin-allergic patients are treated for 10 days with erythromycin, clarithromycin, or clindamycin, or for 5 days with azithromycin.

The increased use of macrolides and related antibiotics for a variety of infections, especially the azalide, azithromycin, is associated with increased rates of resistance to these drugs among GAS in many countries. Approximately 10% of GAS in the United States and more than 10% in Canada are macrolide-resistant (macrolide resistance includes azalide resistance), but there is considerable local variation in both countries. Some macrolide-resistant GAS isolates are also resistant to clindamycin. Although not a major hindrance for treatment of pharyngitis, clindamycin resistance may be important in management of invasive GAS infections. Use of these antibiotics should be restricted to patients who cannot safely receive a β-lactam drug for GAS pharyngitis. Tetracyclines, fluoroquinolones, or sulfonamides should not be used to treat GAS pharyngitis.

**CHRONIC GROUP**

**A STREPTOCOCCUS CARRIERS**

Patients who continue to harbor GAS in the pharynx despite appropriate antibiotic therapy are streptococcal carriers. They have little or no evidence of an immune response to the organism. The pathogenesis of chronic carriage is not known. Carriage generally poses little risk to patients and their contacts, but it can confound testing in subsequent episodes of sore throat. Patients with repeated test-positive pharyngitis create anxiety among their families and physicians. It is usually unnecessary to attempt to eliminate chronic carriage. Instead, evaluation and treatment of pharyngitis should be undertaken without regard for chronic carriage, treating test-positive patients in routine fashion and avoiding antibiotics in patients who have negative tests. Expert opinion suggests that eradication might be attempted in select circumstances: a community outbreak of ARF or APSGN; personal or family history of ARF; an outbreak of GAS pharyngitis in a closed or semiclosed community, nursing home or healthcare facility; repeated episodes of symptomatic GAS pharyngitis in a family with “ping pong” spread among family members despite adequate therapy; when tonsillectomy is being considered because of chronic carriage or recurrent streptococcal pharyngitis; and extreme, unmanageable anxiety related to GAS carriage (“streptophobia”) among family members. Clindamycin given by mouth for 10 days is effective therapy (20 mg/kg/day divided in 3 doses; adult dose 150-450 mg tid). Amoxicillin-clavulanate (40 mg amoxicillin/kg/day up to 2000 mg amoxicillin/day divided tid for 10 days) and 4 days of oral rifampin plus either intramuscular benzathine penicillin given once or oral penicillin given for 10 days have also been used.

**RECURRENT PHARYNGITIS**

True recurrent GAS pharyngitis can occur for several reasons: reinfection with the same M type if type-specific antibody has not developed; poor compliance with oral antibiotic therapy; macrolide resistance if a macrolide was used for treatment; and infection with a new M type. Unfortunately, determining the GAS M type in an acute infection is not available to the clinician. Treatment with intramuscular benzathine penicillin eliminates nonadherence to therapy. Apparent recurrences can represent pharyngitis of another cause in the presence of streptococcal carriage. Chronic GAS carriage is particularly likely if the illnesses are mild and otherwise atypical for GAS pharyngitis. Undocumented histories of recurrent pharyngitis are an inadequate basis for recommending tonsillectomy.

Tonsillectomy may lower the incidence of pharyngitis for 1-2 yr among children with frequent episodes of documented pharyngitis (≥7 episodes in the previous year or ≥5 in each of the preceding 2 yr, or ≥3 in each of the previous 3 yr). However, the frequency of pharyngitis (GAS and non-GAS) generally declines over time. By 2 yr posttonsillectomy the incidence of pharyngitis in severely affected children is
similar among those who have tonsillectomy and those who do not. Few children are so severely affected and the limited clinical benefit of tonsillectomy for most must be balanced against the risks of anesthesia and surgery.

Recurrent GAS pharyngitis is rarely, if ever, a sign of an immune disorder. However, recurrent pharyngitis can be part of a recurrent fever or autoinflammatory syndrome such as PFAPA syndrome. Prolonged pharyngitis (>1 wk) can occur in infectious mononucleosis and Lemierre syndrome, but it also suggests the possibility of another disorder such as neutropenia, a recurrent fever syndrome, or an autoimmune disease such as systemic lupus or inflammatory bowel disease. In such instances, pharyngitis would be one of a number of clinical findings that together should suggest the underlying diagnosis.

**COMPLICATIONS AND PROGNOSIS**

Viral respiratory tract infections can predispose to bacterial middle ear infections and bacterial sinusitis. The complications of GAS pharyngitis include local suppurative complications, such as parapharyngeal abscess, and subsequent nonsuppurative illnesses, such as ARF, APSGN, poststreptococcal reactive arthritis, and possibly PANDAS (pediatric autoimmune neuropsychiatric disorders associated with *S. pyogenes*) or CANS (childhood acute neuropsychiatric symptoms).

**PREVENTION**

A variety of GAS vaccines are being developed. A recombinant multivalent M-type vaccine uses the terminal portions of various M proteins to take advantage of their immunogenicity. Other vaccines are based on more conserved GAS epitopes in order to avoid the necessity of matching the vaccine with the M types prevalent in a community or target population. None of the investigational GAS vaccines are near licensing for use. Antimicrobial prophylaxis with daily oral penicillin prevents recurrent GAS infections but is recommended only to prevent recurrences of ARF.

*Bibliography is available at Expert Consult.*
Chapter 381  Acute Pharyngitis  2021.e1

Bibliography


of the oropharynx. A retropharyngeal abscess can also result from penetrating trauma to the oropharynx, dental infection, and vertebral osteomyelitis. Once infected, the nodes may progress through 3 stages: cellulitis, phlegmon, and abscess. Infection in the retropharyngeal and lateral pharyngeal spaces can result in airway compromise or posterior mediastinitis, making timely diagnosis important.

**RETROPHARYNGEAL AND LATERAL PHARYNGEAL ABSCESS**

Retropharyngeal abscess occurs most commonly in children younger than 3-4 yr of age; as the retropharyngeal nodes involute after 5 yr of age, infection in older children and adults is much less common.

Boys are affected more often than girls and approximately two-thirds of patients have a history of recent ear, nose, or throat infection.

Clinical manifestations of retropharyngeal abscess are nonspecific and include fever, irritability, decreased oral intake, and drooling. Neck stiffness, torticollis, and refusal to move the neck may also be present. The verbal child might complain of sore throat and neck pain. Other signs can include muffled voice, stridor, respiratory distress, or even obstructive sleep apnea. Physical examination can reveal bulging of the posterior pharyngeal wall, although this is present in <50% of infants with retropharyngeal abscess. Cervical lymphadenopathy may also be present. Lateral pharyngeal abscess commonly presents as fever, dysphagia, and a prominent bulge of the lateral pharyngeal wall, sometimes with medial displacement of the tonsil.

The differential diagnosis includes acute epiglottitis and foreign body aspiration. In the young child with limited neck mobility, meningitis must also be considered. Other possibilities include lymphoma, hematoma, and vertebral osteomyelitis.

Incision and drainage and culture of an abscessed node provides the definitive diagnosis, but CT can be useful in identifying the presence of a retropharyngeal, lateral pharyngeal, or parapharyngeal abscess (Figs. 382-1 and 382-2). With CT scans, deep neck infections can be accurately identified and localized, but CT accurately identifies abscess formation in only 63% of patients. Soft-tissue neck films taken during inspiration with the neck extended might show increased width or an air–fluid level in the retropharyngeal space. CT with contrast medium enhancement can reveal central lucency, ring enhancement, or scalloping of the walls of a lymph node. Scalloping of the abscess wall is thought to be a late finding and predicts abscess formation.

Retropharyngeal and lateral pharyngeal infections are most often polymicrobial; the usual pathogens include group A streptococcus (see Chapter 183), oropharyngeal anaerobic bacteria (see Chapter 213), and *Staphylococcus aureus* (see Chapter 181.1). In children younger than age 2 yr, there has been an increase in the incidence of retropharyngeal abscess, particularly with *S. aureus*, including methicillin-resistant strains. Mediastinitis may be identified on CT in some of these patients. Other pathogens can include *Haemophilus influenzae*, *Klebsiella*, and *Mycobacterium avium-intracellulare*.

Treatment options include intravenous antibiotics with or without surgical drainage. A third-generation cephalosporin combined with ampicillin-sulbactam or clindamycin to provide anaerobic coverage is effective. The increasing prevalence of methicillin-resistant *S. aureus* can influence empiric antibiotic therapy. Studies show that >50% of children with retropharyngeal or lateral pharyngeal abscesses as identified by CT can be successfully treated without surgical drainage. Drainage is necessary in the patient with respiratory distress or failure to improve with intravenous antibiotic treatment. The optimal duration of treatment is unknown, but therapy for several days with intravenous antibiotics until the patient has begun to improve followed by a course of oral antibiotic is typically used.

Complications of retropharyngeal or lateral pharyngeal abscess include significant upper airway obstruction, rupture leading to aspiration pneumonia, and extension to the mediastinum. Thrombophlebitis of the internal jugular vein and erosion of the carotid artery sheath can also occur.

An uncommon but characteristic infection of the parapharyngeal space is Lemierre disease, in which infection from the oropharynx extends to cause septic thrombophlebitis of the internal jugular vein
Respiratory System

An asymmetric tonsillar bulge with displacement of the uvula. An asymmetric tonsillar bulge is diagnostic, but it may be poorly visualized because of trismus. CT is helpful for revealing the abscess. Group A streptococci and mixed oropharyngeal anaerobes are the most common pathogens, with more than 4 bacterial isolates per abscess typically recovered by needle aspiration.

Treatment includes surgical drainage and antibiotic therapy effective against group A streptococci and anaerobes. Surgical drainage may be accomplished through needle aspiration, incision and drainage, or tonsillectomy. Needle aspiration can involve aspiration of the superior, middle, and inferior aspects of the tonsil to locate the abscess. Intraoral ultrasound can be used to diagnose and guide needle aspiration of a peritonsillar abscess. General anesthesia may be required for the uncooperative patient. Approximately 95% of peritonsillar abscesses resolve after needle aspiration and antibiotic therapy. A small percentage of these patients require a repeat needle aspiration. The 5% with infections that fail to resolve after needle aspiration require incision and drainage. Tonsillectomy should be considered if there is failure to improve within 24 hr of antibiotic therapy and needle aspiration.

**PERITONSILLAR CELLULITIS AND/OR ABSCESS**

Peritonsillar cellulitis and/or abscess, which is relatively common compared to the deep neck infections, is caused by bacterial invasion through the capsule of the tonsil, leading to cellulitis and/or abscess formation in the surrounding tissues. The typical patient with a peritonsillar abscess is an adolescent with a recent history of acute pharyngotonsillitis. Clinical manifestations include sore throat, fever, trismus, and dysphagia. Physical examination reveals an asymmetric tonsillar bulge with displacement of the uvula. An asymmetric tonsillar bulge is diagnostic, but it may be poorly visualized because of trismus. CT is helpful for revealing the abscess. Group A streptococci and mixed oropharyngeal anaerobes are the most common pathogens, with more than 4 bacterial isolates per abscess typically recovered by needle aspiration. Treatment includes surgical drainage and antibiotic therapy effective against group A streptococci and anaerobes. Surgical drainage may be accomplished through needle aspiration, incision and drainage, or tonsillectomy. Needle aspiration can involve aspiration of the superior, middle, and inferior aspects of the tonsil to locate the abscess. Intraoral ultrasound can be used to diagnose and guide needle aspiration of a peritonsillar abscess. General anesthesia may be required for the uncooperative patient. Approximately 95% of peritonsillar abscesses resolve after needle aspiration and antibiotic therapy. A small percentage of these patients require a repeat needle aspiration. The 5% with infections that fail to resolve after needle aspiration require incision and drainage. Tonsillectomy should be considered if there is failure to improve within 24 hr of antibiotic therapy and needle aspiration.

**Figure 382-1** CT of retropharyngeal abscess. A, CT image at level of epiglottis. B, Sequential CT slice exhibiting ring-enhancing lesion. C, Further sequential CT slice demonstrating inferior extent of lesion. (From Philpott CM, Selvadurai D, Banerjee AR: Paediatric retropharyngeal abscess, J Laryngol Otol 118:925, 2004.)

**Figure 382-2** CT of parapharyngeal abscess in a 3 yr old child. A, Sagittal section demonstrating parapharyngeal abscess (A) and mucosal swelling (M) in the maxillary sinus. B, Coronal section of parapharyngeal abscess (A).
A history of recurrent peritonsillar abscess or recurrent tonsillitis, or complications from peritonsillar abscess. The feared, albeit rare, complication is rupture of the abscess, with resultant aspiration pneumonia. There is a 10% recurrence risk for peritonsillar abscess.

Bibliography is available at Expert Consult.
Bibliography


ANATOMY

The Waldeyer ring (the lymphoid tissue surrounding the opening of the oral and nasal cavities into the pharynx) comprises the palatine tonsils, the pharyngeal tonsil or adenoid, lymphoid tissue surrounding the eustachian tube orifice in the lateral walls of the nasopharynx, the lingual tonsil at the base of the tongue, and scattered lymphoid tissue throughout the remainder of the pharynx, particularly behind the posterior pharyngeal pillars and along the posterior pharyngeal wall. The palatine tonsil consists of lymphoid tissue located between the palatoglossal fold (anterior tonsillar pillar) and the palatopharyngeal fold (posterior tonsillar pillar) forms. This lymphoid tissue is separated from the surrounding pharyngeal musculature by a thick fibrous capsule. The adenoid is a single aggregation of lymphoid tissue that occupies the space between the nasal septum and the posterior pharyngeal wall. A thin fibrous capsule separates it from the underlying structures; the adenoid does not contain the complex crypts that are found in the palatine tonsils but rather more simple crypts. Lymphoid tissue at the base of the tongue forms the lingual tonsil that also contains simple tonsillar crypts.

NORMAL FUNCTION

Located at the opening of the pharynx to the external environment, the tonsils and adenoid are well situated to provide primary defense against foreign matter. The immunologic role of the tonsils and adenoids is to induce secretory immunity and to regulate the production of the secretory immunoglobulins. Deep crevices within tonsillar tissue form tonsillar crypts that are lined with squamous epithelium and host a concentration of lymphocytes at their bases. The lymphoid tissue of the Waldeyer ring is most immunologically active between 4 and 10 yr of age, with a decrease after puberty. Adenotonsillar hypertrophy is greatest between ages 3 and 6 yr; in most children tonsils begin to involute after age 8 yr. No major immunologic deficiency has been demonstrated after removal of either or both of the tonsils and adenoid.

PATHOLOGY

Acute Infection

Most episodes of acute pharyngotonsillitis are caused by viruses (see Chapter 381). Group A β-hemolytic streptococcus (GABHS) is the most common cause of bacterial infection in the pharynx (see Chapter 183).

Chronic Infection

The tonsils and adenoids can be chronically infected by multiple microbes, which can include a high incidence of β-lactamase–producing organisms. Both aerobic species, such as streptococci and Haemophilus influenzae, and anaerobic species, such as Peptostreptococcus, Prevotella, and Fusobacterium, contribute. The tonsillar crypts can accumulate desquamated epithelial cells, lymphocytes, bacteria, and other debris, causing cryptic tonsillitis. With time, these cryptic plugs can calcify into tonsillar concretions or tonsillolith. Biofilms appear to play a role in chronic inflammation of the tonsils.

Airway Obstruction

Both the tonsils and adenoids are a major cause of upper airway obstruction in children. Airway obstruction in children is typically manifested in sleep-disordered breathing, including obstructive sleep apnea, obstructive sleep hypopnea, and upper airway resistance syndrome (see Chapter 19). Sleep-disordered breathing secondary to adenotonsillar breathing is a cause of growth failure (see Chapter 41).

Tonsillar Neoplasm

Rapid enlargement of one tonsil is highly suggestive of a tonsillar malignancy, typically lymphoma in children.

CLINICAL MANIFESTATIONS

Acute Infection

Symptoms of GABHS infection include odynophagia, dry throat, malaise, fever and chills, dysphagia, referred otalgia, headache, muscular aches, and enlarged cervical nodes. Signs include dry tongue, erythematous enlarged tonsils, tonsillar or pharyngeal exudate, palatine petechiae, and enlargement and tenderness of the jugulodigastric lymph nodes (Fig. 383-1; see Chapters 183 and 381).

Chronic Infection

Children with chronic or cryptic tonsillitis often present with halitosis, chronic sore throats, foreign-body sensation, or a history of expelling foul-tasting and foul-smelling cheesy lumps. Examination reveals
tonsils of a range of sizes which often they contain copious debris within the crypts. The offending organism is not usually GABHS.

**Airway Obstruction**

The diagnosis of airway obstruction (see Chapter 19) can frequently be made by history and physical examination. Daytime symptoms of airway obstruction, secondary to adenotonsillar hypertrophy, include chronic mouth breathing, nasal obstruction, hyponasal speech, hypomania, decreased appetite, poor school performance, and, rarely, symptoms of right-sided heart failure. Nighttime symptoms consist of loud snoring, choking, gasping, frank apnea, restless sleep, abnormal sleep positions, somnambulism, night terrors, diaphoresis, enuresis, and sleep talking. Large tonsils are typically seen on examination, although the absolute size might not indicate the degree of obstruction. The size of the adenoid tissue can be demonstrated on a lateral neck radiograph or with flexible endoscopy. Other signs that can contribute to airway obstruction include the presence of a craniofacial syndrome or hypotonia.

**Tonsillar Neoplasm**

The rapid unilateral enlargement of a tonsil, especially if accompanied by systemic signs of night sweats, fever, weight loss, and lymphadenopathy, is highly suggestive of a tonsillar malignancy. The diagnosis of a tonsil malignancy should also be entertained if the tonsil appears grossly abnormal. Among 54,901 patients undergoing tonsillectomy, 54 malignancies were identified (0.087% prevalence); but all 6 malignancies had been suspected based on suspicious anatomic features preoperatively.

**TREATMENT**

**Medical Management**

The treatment of acute pharyngotonsillitis is discussed in Chapter 381 and antibiotic treatment of GABHS in Chapter 183. Because copathogens such as staphylococci or anaerobes can produce β-lactamase that can inactivate penicillin, the use of cephalosporins or clindamycin may be more efficacious in the treatment of chronic throat infections. Tonsillolith or debris may be expressed manually with either a cotton-tipped applicator or a water jet. Chronically infected tonsillar crypts can be cauterized using silver nitrate.

**Tonsillectomy**

Tonsillectomy alone is most commonly performed for recurrent or chronic pharyngotonsillitis. Tonsillectomy has been shown to be effective in reducing the number of infections and the symptoms of chronic tonsillitis such as halitosis, persistent or recurrent sore throats, and recurrent cervical adenitis. In resistant cases of cryptic tonsillitis, tonsillectomy may be curative. Rarely in children, tonsillectomy is indicated for biopsy of a unilaterally enlarged tonsil to exclude a neoplasm or to treat recurrent hemorrhage from superficial tonsillar blood vessels. Tonsillectomy has not been shown to offer clinical benefit over conservative treatment in children with mild symptoms.

There are large variations in surgical rates among children across countries: 144 in 10,000 in Italy; 115 in 10,000 in the Netherlands; 65 in 10,000 in England; and 50 in 10,000 in the United States. Rates are generally higher in boys. With the issuance of practice guidelines, these variations may decrease. The American Academy of Otolaryngology (AAO)–Head and Neck Surgery Taskforce on Clinical Practice Guidelines: Tonsillectomy in Children issued evidence-based guidelines in 2011 (Table 383-1). Table 383-2 illustrates the differences and

<table>
<thead>
<tr>
<th>Table 383-1: Paradise Criteria for Tonsillectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRITERION</strong></td>
</tr>
<tr>
<td>Minimum frequency of sore throat episodes</td>
</tr>
<tr>
<td>Clinical features</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Documentation</td>
</tr>
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</table>

### Table 383-2: Comparison of American, Italian, and Scottish Guidelines for Tonsillectomy in Children and Adolescents

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>AAO-HNS GUIDELINES</th>
<th>ITALIAN GUIDELINES</th>
<th>SCOTTISH GUIDELINES</th>
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<tr>
<td>Audience</td>
<td>Multidisciplinary</td>
<td>Multidisciplinary</td>
<td>Multidisciplinary</td>
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<tr>
<td>Target population</td>
<td>Children and adolescents 1-18 yr of age</td>
<td>Children and adults</td>
<td>Children 4-16 yr of age and adults</td>
</tr>
<tr>
<td>Scope</td>
<td>Treatment of children who are candidates for tonsillectomy</td>
<td>Appropriateness and safety of tonsillectomy</td>
<td>Management of sore throat and indications for tonsillectomy</td>
</tr>
<tr>
<td>Methods</td>
<td>Based on a priori protocol, systematic literature review, American Academy of Pediatrics scale of evidence quality</td>
<td>Systematic literature review, Italian National Program Guidelines scale of evidence quality</td>
<td>Based on a priori protocol, systematic literature review, Scottish Intercollegiate Guidelines Network scale of evidence quality</td>
</tr>
<tr>
<td>Recommendations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>Tonsillectomy is an option for children with recurrent throat infection that meets the Paradise criteria (see Table 383-1) for frequency, severity, treatment, and documentation of illness</td>
<td>Tonsillectomy is indicated in patients with at least 1 yr of recurrent tonsillitis (5 or more episodes per year) that is disabling and impairs normal activities, but only after an additional 6 mo of watchful waiting to assess the pattern of symptoms using a clinical diary</td>
<td>Tonsillectomy should be considered for recurrent, disabling sore throat caused by acute tonsillitis when the episodes are well documented, are adequately treated, and meet the Paradise criteria (see Table 383-1) for frequency of illness</td>
</tr>
<tr>
<td>Pain control</td>
<td>Recommendation to advocate for pain relief (e.g., provide information, prescribe) and educate caregivers about the importance of managing and reassessing pain</td>
<td>Recommendation for acetaminophen before and after surgery</td>
<td>Recommendation for adequate dose of acetaminophen for pain relief in children</td>
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<tr>
<td>Antibiotic use</td>
<td>Recommendation against perioperative antibiotics</td>
<td>Recommendation for short-term perioperative antibiotics*</td>
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<td>Steroid use</td>
<td>Recommendation for a single intraoperative dose of dexamethasone</td>
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<td>NA</td>
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<td>Sleep-disordered breathing</td>
<td>Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with sleep-disordered breathing and comorbid conditions</td>
<td>Recommendation for diagnostic testing in children with suspected sleep respiratory disorders</td>
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<td>Polysomnography</td>
<td>Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with abnormal polysomnography</td>
<td>Recommendation for polysomnography when pulse oximetry results are not conclusive in agreement with Brouillette criteria</td>
<td>NA</td>
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<tr>
<td>Surgical technique</td>
<td>NA</td>
<td>Recommendation for “cold” technique</td>
<td>NA</td>
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<tr>
<td>Hemorrhage</td>
<td>Recommendation that the surgeon document primary and secondary hemorrhage after tonsillectomy at least annually</td>
<td>NA</td>
<td>NA</td>
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<td>Adjunctive therapy</td>
<td>NA</td>
<td>NA</td>
<td>Recommendation against Echinacea purpurea for treatment of sore throat Recommendation for acupuncture in patients at risk of postoperative nausea and vomiting who cannot take antiemetic drugs</td>
</tr>
</tbody>
</table>

*Statement made prior to most recent Cochrane review.

AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; NA, not applicable.

Adenoidectomy alone may be indicated for the treatment of chronic nasal infection (chronic adenoiditis), chronic sinus infections that have failed medical management, and recurrent bouts of acute otitis media, including those in children with tympanostomy tubes who suffer from recurrent otorrhea. Adenoidectomy may be helpful in children with chronic or recurrent otitis media with effusion. Adenoidectomy alone may be curative in the management of patients with nasal obstruction, chronic mouth breathing, and loud snoring suggesting sleep-disordered breathing. Adenoidectomy may also be indicated for children in whom upper airway obstruction is suspected of causing craniofacial or occlusive developmental abnormalities.
Tonsillectomy and Adenoidectomy

The criteria for both tonsillectomy and adenoidectomy for recurrent infection are the same as those for tonsillectomy alone. The other major indication for performing both procedures together is upper airway obstruction secondary to adenotonsillar hypertrophy that results in sleep-disordered breathing, failure to thrive, craniofacial or occlusive developmental abnormalities, speech abnormalities, or, rarely, cor pulmonale. A high proportion of children with failure to thrive in the context of adenotonsillar hypertrophy resulting in sleep disorder experiences significant growth acceleration after adenotonsillectomy.

COMPLICATIONS

Poststreptococcal Glomerulonephritis and Acute Rheumatic Fever

The 2 major complications of untreated GABHS infection are poststreptococcal glomerulonephritis and acute rheumatic fever (see Chapters 511.1 and 183).

Peritonsillar Infection

Peritonsillar infection can occur as either cellulitis or a frank abscess in the region superior and lateral to the tonsillar capsule (see Chapter 381). These infections usually occur in children with a history of recurrent tonsillar infection and are polymicrobial, including both aerobes and anaerobes. Unilateral throat pain, referred otalgia, drooling, and trismus are presenting symptoms. The affected tonsil is displaced down and medial by swelling of the anterior tonsillar pillar and palate. The diagnosis of an abscess can be confirmed by CT or by needle aspiration, the contents of which should be sent for culture.

Retropharyngeal Space Infection

Infections in the retropharyngeal space develop in the lymph nodes that drain the oropharynx, nose, and nasopharynx (see Chapter 382).

Parapharyngeal Space Infection

Tonsillar infection can extend into the parapharyngeal space, causing symptoms of fever, neck pain and stiffness, and signs of swelling of the lateral pharyngeal wall and neck on the affected side. The diagnosis is confirmed by contrast medium–enhanced CT, and treatment includes intravenous antibiotics and external incision and drainage if an abscess is demonstrated on CT (see Chapter 382). Septic thrombophlebitis of the jugular vein, Lemierre syndrome, manifests with fever, toxicity, neck pain and stiffness, and respiratory distress as a result of multiple septic pulmonary emboli and is a complication of a parapharyngeal space or odontogenic infection from Fusobacterium necrophorum. Concurrent Epstein-Barr virus mononucleosis (see Chapter 254) can be a predisposing event before the sudden onset of fever, chills, and respiratory distress in an adolescent patient. Treatment includes high-dose intravenous antibiotics (ampicillin-sulbactam, clindamycin, penicillin, or ciprofloxacin) and heparinization.

Recurrent or Chronic Pharyngotonsillitis

See Chapter 381.

CHRONIC AIRWAY OBSTRUCTION

Although rare, children with chronic airway obstruction from enlarged tonsils and adenoids can present with cor pulmonale.

The effects of chronic airway obstruction and mouth breathing on facial growth remain a subject of controversy. Studies of chronic mouth breathing, both in humans and animals, have shown changes in facial development, including prolongation of the total anterior facial height and a tendency toward a retrognathic mandible, the so-called adenoid facies. Adenotonsillectomy can reverse some of these abnormalities. Other studies have disputed these findings.

Tonsillectomy and Adenoidectomy

The risks and potential benefits of surgery must be considered (Table 383-3). Bleeding can occur in the immediate postoperative period or be delayed (consider von Willebrand disease) after separation of the eschar. The Clinical Guidelines for Tonsillectomy include a recommendation for a single intravenous dose of intraoperative dexamethasone (0.5 mg/kg), which decreases postoperative nausea and vomiting and reduces swelling. There is no evidence that use of dexamethasone in postoperative tonsillectomy patients results in an increased risk of postoperative bleeding. Routine use of antibiotics in the postoperative period is ineffective and thus the American Academy of Otolaryngology Clinical Practice Guidelines advise against its use, although this recommendation is not consistent among the major professional organizations who have issued guidelines (see Table 383-2). Codeine is associated with excessive sedation and fatalities and is not recommended.

Swelling of the tongue and soft palate can lead to acute airway obstruction in the 1st few hr after surgery. Children with underlying hypoventilation or craniofacial anomalies are at greater risk for suffering this complication. Dehydration from odynophagia is not uncommon in the 1st postoperative week. Rare complications include velopharyngeal insufficiency, nasopharyngeal or oropharyngeal stenosis, and psychological problems.

Bibliography is available at Expert Consult.
Bibliography


Respiratory tract symptoms, including cough, wheeze, and stridor, occur frequently or persist for long periods in a substantial number of children; other children have persistent or recurring lung infiltrates with or without symptoms. Determining the cause of these chronic findings can be difficult because symptoms can be caused by a close succession of unrelated acute respiratory tract infections or by a single pathophysiologic process. Specific and easily performed diagnostic tests do not exist for many acute and chronic respiratory conditions. Pressure from the affected child's family for a quick remedy because of concern over symptoms related to breathing may complicate diagnostic and therapeutic efforts.

A systematic approach to the diagnosis and treatment of these children consists of assessing whether the symptoms are the manifestation of a minor problem or a life-threatening process; determining the most likely underlying pathogenic mechanism; selecting the simplest effective therapy for the underlying process, which often is only symptomatic therapy; and carefully evaluating the effect of therapy. Failure of this approach to identify the process responsible or to effect improvement signals the need for more extensive and perhaps invasive diagnostic efforts, including bronchoscopy.

**JUDGING THE SERIOUSNESS OF CHRONIC RESPIRATORY COMPLAINTS**

Clinical manifestations suggesting that a respiratory tract illness may be life-threatening or associated with the potential for chronic disability are listed in Table 384-1. If none of these findings is detected, the chronic respiratory process is more likely to be benign. Active, well-nourished, and appropriately growing infants who present with intermittent noisy breathing but no other physical or laboratory abnormalities require only symptomatic treatment and parental reassurance. Benign-appearing but persistent symptoms are occasionally the harbinger of a serious lower respiratory tract problem. By contrast, occasionally children (e.g., infection-related asthma) have recurrent life-threatening episodes but few or no symptoms in the intervals. Repeated examinations over an extended period, both when the child appears healthy and when the child is symptomatic, may be helpful in sorting out the severity and chronicity of lung disease.

**RECURRENT OR PERSISTENT COUGH**

Cough is a reflex response of the lower respiratory tract to stimulation of irritant or cough receptors in the airways’ mucosa. The most common cause in children is airway reactivity (asthma). Because cough receptors also reside in the pharynx, paranasal sinuses, stomach, and external auditory canal, the source of a persistent cough may need to be sought beyond the lungs. Specific lower respiratory stimuli include excessive secretions, aspirated foreign material, inhaled dust particles or noxious gases, cold or dry air, and an inflammatory response to infectious agents or allergic processes. Table 384-2 lists some of the conditions responsible for chronic cough.

Table 384-3 presents characteristics of cough that can aid in distinguishing a cough’s origin. Additional useful information can include a history of atopic conditions (asthma, eczema, urticaria, allergic rhinitis), a seasonal or environmental variation in frequency or intensity of cough, and a strong family history of atopic conditions, all suggesting an allergic cause; symptoms of malabsorption or family history indicating cystic fibrosis; symptoms related to feeding, suggesting aspiration or gastroesophageal reflux; a choking episode, suggesting foreign-body aspiration; headache or facial edema associated with sinusitis; and a smoking history in older children and adolescents or the presence of a smoker in the house (Table 384-4).

The physical examination can provide much information pertaining to the cause of chronic cough. Posterior pharyngeal drainage combined with a nighttime cough suggests chronic upper airway disease such as sinusitis. An overinflated chest suggests chronic airway obstruction, as
in asthma or cystic fibrosis. An expiratory wheeze, with or without diminished intensity of breath sounds, strongly suggests asthma or asthmatic bronchitis but may also be consistent with a diagnosis of cystic fibrosis, bronchomalacia, vascular ring, aspiration of foreign material, or pulmonary hemosiderosis. Careful auscultation during forced expiration may reveal expiratory wheezes that are otherwise undetectable and that are the only indication of underlying reactive airways. Coarse crackles suggest bronchiectasis, including cystic fibrosis, but can also occur with an acute or subacute exacerbation of asthma. Clubbing of the digits is seen in most patients with bronchiectasis but in only a few other respiratory conditions with chronic cough (see Table 384-2). Tracheal deviation suggests foreign body aspiration or a mediastinal mass.

Allowing sufficient examination time to detect a spontaneous cough is important. If a spontaneous cough does not occur, asking the child to take a maximal breath and forcefully exhale repeatedly usually induces a cough reflex. Most children can cough on request by 4-5 yr of age. Children who cough as often as several times a day, never during sleep, may also be consistent with a diagnosis of cystic fibrosis or bronchial asthma.

### Table 384-3

**Characteristics of Cough and Other Clinical Features and Possible Causes**

<table>
<thead>
<tr>
<th>SYMPTOMS AND SIGNS</th>
<th>POSSIBLE UNDERLYING ETIOLOGY*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auscultatory findings (wheeze, crepitations/crackles, differential breath sounds)</td>
<td>Asthma, bronchitis, congenital lung disease, foreign body aspiration, airway abnormality</td>
</tr>
<tr>
<td>Cough characteristics (e.g., cough with choking, cough quality, cough starting from birth)</td>
<td>See text; congenital lung abnormalities</td>
</tr>
<tr>
<td>Cardiac abnormalities (including murmurs)</td>
<td>Any cardiac illness</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Asthma, functional, pleuritis</td>
</tr>
<tr>
<td>Chest wall deformity</td>
<td>Any chronic lung disease</td>
</tr>
<tr>
<td>Digital clubbing</td>
<td>Suppurative lung disease, arteriovenous shunt</td>
</tr>
<tr>
<td>Dyspnea (exertional or at rest)</td>
<td>Compromised lung function of any chronic lung or cardiac disease</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Compromised lung function, immunodeficiency, cystic fibrosis</td>
</tr>
<tr>
<td>Feeding difficulties (including choking and vomiting)</td>
<td>Compromised lung function, aspiration</td>
</tr>
<tr>
<td>Hemoptyisis</td>
<td>Bronchitis, foreign body aspiration, suctioning trauma</td>
</tr>
<tr>
<td>Immune deficiency</td>
<td>Atypical and typical recurrent respiratory infections</td>
</tr>
<tr>
<td>Medications or drugs</td>
<td>Angiotensin-converting enzyme inhibitors, puffers, illicit drug use</td>
</tr>
<tr>
<td>Neurodevelopmental abnormality</td>
<td>Aspiration</td>
</tr>
<tr>
<td>Recurrent pneumonia</td>
<td>Immunodeficiency, congenital lung problem, airway abnormality</td>
</tr>
<tr>
<td>Symptoms of upper respiratory tract infection</td>
<td>Can coexist or be a trigger for an underlying problem</td>
</tr>
</tbody>
</table>

*This is not an exhaustive list; only the more common respiratory diseases are mentioned.


### Table 384-4

**Clinical Clues About Cough**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>THINK OF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staccato, paroxysmal</td>
<td>Pertussis, cystic fibrosis, foreign body, Chlamydia spp., Mycoplasma spp.</td>
</tr>
<tr>
<td>Followed by “whoop”</td>
<td>Pertussis</td>
</tr>
<tr>
<td>All day, never during sleep</td>
<td>Habit cough</td>
</tr>
<tr>
<td>Barking, brassy</td>
<td>Croup, habit cough, tracheomalacia, tracheitis, epiglottitis</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Laryngeal involvement (croup, recurrent laryngeal nerve involvement)</td>
</tr>
<tr>
<td>Abrupt onset</td>
<td>Foreign body, pulmonary embolism</td>
</tr>
<tr>
<td>Follows exercise</td>
<td>Reactive airway disease</td>
</tr>
<tr>
<td>Accompanies eating, drinking</td>
<td>Aspiration, gastroesophageal reflux, tracheoesophageal fistula</td>
</tr>
<tr>
<td>Throat clearing</td>
<td>Postnasal drip, vocal tic</td>
</tr>
<tr>
<td>Productive (sputum)</td>
<td>Infection, cystic fibrosis, bronchiectasis</td>
</tr>
<tr>
<td>Night cough</td>
<td>Sinusitis, reactive airway disease, gastroesophageal reflux</td>
</tr>
<tr>
<td>Seasonal</td>
<td>Allergic rhinitis, reactive airway disease</td>
</tr>
<tr>
<td>Immunosuppressed patient</td>
<td>Bacterial pneumonia, Pneumocystis jiroveci, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, cytomegalovirus</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Hypoxia, hypercarbia</td>
</tr>
<tr>
<td>Animal exposure</td>
<td>Chlamydia psittaci (birds), Yersinia pestis (rodents), Francisella tularensis (rabbits), Q fever (sheep, cattle), hantavirus (rodents), histoplasmosis (pigeons)</td>
</tr>
<tr>
<td>Geographic</td>
<td>Histoplasmosis (Mississippi, Missouri, Ohio River Valley), coccidioidomycosis (Southwest), blastomycosis (North and Midwest)</td>
</tr>
<tr>
<td>Workdays with clearing on days off</td>
<td>Occupational exposure</td>
</tr>
</tbody>
</table>

causes of recurrent or persistent stridor

However, acquire recurrent stridor or have persistent stridor from the bodies and trauma can also cause acute stridor. A few children, commonly observed in children with croup (see chapter 384); foreign accompanied by a croupy cough and hoarse voice. Stridor is most a harsh, medium-pitched, inspiratory sound associated with aspiration. Rarely, children may expectorate partial casts of the airway which can be characterized in investigating causes of plastic bronchitis. Children whose coughs persist for more than 6 wk should be tested for cystic fibrosis regardless of their race or ethnicity (see chapter 403). Sputum culture is helpful in evaluation of cystic fibrosis, but less so for other conditions because throat flora can contaminate the sample.

Hematologic assessment can reveal a microcytic anemia that is the result of pulmonary hemosiderosis (see chapter 406) or hemosedisis, or eosinophilia that accompanies asthma and other hypersensitivity reactions of the lung. Infiltrates on the chest radiograph suggest cystic fibrosis, bronchiectasis, foreign body, hypersensitivity pneumonia, or tuberculosis. When asthma-equivalent cough is suggested, a trial of bronchodilator therapy may be diagnostic. If the cough does not respond to initial therapeutic efforts, more-specific diagnostic procedures may be warranted, including an immunologic or allergic evaluation, chest and paranasal sinus imaging, esophagograms, tests for gastroesophageal reflux (see chapter 323), and special microbiologic studies including rapid viral testing. Evaluation of ciliary morphology, nasal endoscopy, laryngoscopy and bronchoscopy may also be indicated.

Habit cough (“psychogenic cough” or “cough tic”) must be considered in any child with a cough that has lasted for weeks or months, that has been refractory to treatment, and that disappears with sleep or with distraction. Typically, the cough is abrupt and loud and has a harsh, honking, or “barking” quality. A disassociation between the intensity of the cough and the child’s affect is typically striking. This cough may be absent if the physician listens outside the examination room, but it will reliably appear immediately on direct attention to the child and the symptom. It typically begins with an upper respiratory infection but then lingers. The child misses many days of school because the cough disrupts the classroom. This disorder accounts for many unnecessary medical procedures and courses of medication. It is treatable with assurance that a pathologic lung condition is absent and that the child should resume full activity, including school. This assurance, together with speech therapy techniques that allow the child to reduce musculoskeletal tension in the neck and chest and that increase the child’s awareness of the initial sensations that trigger cough, has been very successful. Self-hypnosis is another successful therapy, often effective with 1 session. The designation “habit cough” is preferable to “psychogenic cough” because it carries no stigma and because most of these children do not have significant emotional problems. When the cough disappears, it does not reemerge as another symptom. Nonetheless, other symptoms such as irritable bowel syndrome may be present in the patient or family.

**FREQUENTLY RECURRING OR PERSISTENT STRIDOR**

Stridor, a harsh, medium-pitched, inspiratory sound associated with obstruction of the laryngeal area or the extrathoracic trachea, is often accompanied by a coughy cough and hoarse voice. Stridor is most commonly observed in children with croup (see chapter 385); foreign bodies and trauma can also cause acute stridor. A few children, however, acquire recurrent stridor or have persistent stridor from the 1st days or weeks of life (table 384-5). Most congenital anomalies of large airways that produce stridor become symptomatic soon after birth. Increase of stridor when a child is supine suggests laryngomalacia or tracheomalacia. It is important to note that when evaluating for a specific anatomic cause of abnormal breath sounds, it is not uncommon to identify additional congenital anomalies of the airway. An accompanying history of hoarseness or aphonia suggests involvement of the vocal cords. Associated dysphagia may also suggest a vascular ring. In a child with intermittent stridor that accompanies physical activity and is not responsive to asthma therapies, paradoxical vocal cord dysfunction may be of consideration. Paradoxical vocal cord dysfunction may be highly supported by history and confirmed by laryngoscopy during an exercise challenge test if symptoms are successfully elicited. Speech therapy and behavior modification may be therapeutic.

Physical examination for recurrent or persistent stridor is usually unrewarding, although changes in its severity and intensity due to changes of body position should be assessed. Anteroposterior and lateral radiographs, contrast esophagography, fluoroscopy, CT, and MRI are potentially useful diagnostic tools. In most cases, direct observation by laryngoscopy is necessary for definitive diagnosis. Undistorted views of the larynx are best obtained with fiberoptic laryngoscopy.

**RECURRENT OR PERSISTENT WHEEZE**

see also chapter 391.

Parents often complain that their child “wheezes,” when, in fact, they are reporting respiratory sounds that are audible without a stethoscope, produce palpable resonance throughout the chest, and occur most
prominently in inspiration. Some of these children have stridor, although many have audible sounds when the supraglottic airway is incompletely cleared of feedings or secretions.

True wheezing is a relatively common and particularly troublesome manifestation of obstructive lower respiratory tract disease in children. The site of obstruction may be anywhere from the intrathoracic trachea to the small bronchi or large bronchioles, but the sound is generated by turbulence in larger airways that collapse with forced expiration (see Chapter 373). Children younger than 2-3 yr are especially prone to wheezing, because bronchospasm, mucosal edema, and accumulation of excessive secretions have a relatively greater obstructive effect on their smaller airways. In addition, the compliant airways in young children collapse more readily with active expiration. Isolated episodes of acute wheezing, such as can occur with bronchiolitis, are not uncommon, but wheezing that recurs or persists for more than 4 wk suggests other diagnoses (see Table 391-1 in Chapter 391). Most recurrent or persistent wheezing in children is the result of airway reactivity. Non-specific environmental factors such as cigarette smoke may be important contributors.

Frequently recurring or persistent wheezing starting at or soon after birth suggests a variety of other diagnoses, including congenital structural abnormalities involving the lower respiratory tract or tracheobronchomalacia (see Chapter 386.11). Wheezing that attends cystic fibrosis is most common in the 1st yr of life. Sudden onset of severe wheezing in a previously healthy child should suggest foreign-body aspiration.

Either wheezing or coughing when associated with tachypnea and hypoxemia may be suggestive of interstitial lung disease (see Chapter 399.5). However, many patients with interstitial lung disease demonstrate no symptoms other than rapid breathing on initial physical examination. Although chest roentgenograms may be normal in interstitial lung disease, diffuse abnormalities on chest X-ray may support further evaluation in patients suspected to have interstitial lung disease with characteristic findings described on high-resolution CT scan and lung biopsy.

Repeated examination may be required to verify a history of wheezing in a child with episodic symptoms and should be directed toward assessing air movement, ventilatory adequacy, and evidence of chronic lung disease, such as fixed overinflation of the chest, growth failure, and digital clubbing. Patients should be assessed for oropharyngeal dysphagia in cases of suspected recurrent aspiration. Clubbing suggests chronic lung infection and is rarely prominent in uncomplicated asthma. Tracheal deviation from foreign body aspiration should be sought. It is essential to rule out wheezing secondary to congestive heart failure. Allergic rhinitis, urticaria, eczema, or evidence of ichthyosis vulgaris suggests asthma or asthmatic bronchitis. The nose should be examined for polyps, which can exist with allergic conditions or cystic fibrosis.

Sputum eosinophilia and elevated serum immunoglobulin E levels suggest allergic reactions. A forced expiratory volume in 1 sec increase of 15% in response to bronchodilators confirms reactive airways. Specific microbiologic studies, special imaging studies of the airways and cardiovascular structures, diagnostic studies for cystic fibrosis, and bronchoscopy (see Chapter 366) should be considered if the response is unsatisfactory.

### Table 384-6 Diseases Associated with Recurrent, Persistent, or Migrating Lung Infiltrates Beyond the Neonatal Period

<table>
<thead>
<tr>
<th>Condition</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration</td>
<td>Pharyngeal incompetence (e.g., cleft palate)</td>
</tr>
<tr>
<td>Laryngotracheosophageal cleft</td>
<td>Tracheosophageal fistula</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Lipid aspiration</td>
</tr>
<tr>
<td>Neurologic dysphagia</td>
<td>Developmental dysphagia</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>Lung cysts (cystic adenomatoid malformation)</td>
</tr>
<tr>
<td>Pulmonary sequestration</td>
<td>Bronchial stenosis or aberrant bronchus</td>
</tr>
<tr>
<td>Vascular ring</td>
<td>Congenital heart disease with large left-to-right shunt</td>
</tr>
<tr>
<td>Pulmonary lymphangiectasis</td>
<td>Genus cerebri</td>
</tr>
<tr>
<td>Asthma</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Primary ciliary dyskinesia (Kartagener syndrome)</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>Sickle cell disease (acute chest syndrome)</td>
</tr>
<tr>
<td>Pulmonary hemosiderosis</td>
<td>Immunodeficiency, phagocytic deficiency</td>
</tr>
<tr>
<td>Collagen-vascular diseases</td>
<td>Humoral, cellular, combined immunodeficiency states</td>
</tr>
<tr>
<td>Infection, congenital</td>
<td>Chronic granulomatous disease and related phagocytic defects</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Complement deficiency states</td>
</tr>
<tr>
<td>Rubella</td>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Asthma</td>
</tr>
<tr>
<td>Infection, acquired</td>
<td>Allergic bronchopulmonary aspergillosi</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Pulmonary hemosiderosis</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Interstitial pneumonitis and fibrosis</td>
</tr>
<tr>
<td>HIV</td>
<td>Usual interstitial pneumonitis</td>
</tr>
<tr>
<td>Other viruses</td>
<td>Lymphoid (AIDS)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Genetic disorders of surfacetant synthesis, secretion</td>
</tr>
<tr>
<td>Mycoplasma, Ureaplasma</td>
<td>Desquamative</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Acute (Hamman-Rich)</td>
</tr>
<tr>
<td>Fungal organisms</td>
<td>Alveolar proteinosis</td>
</tr>
<tr>
<td>Pneumocystis jiroveci</td>
<td>Drug-induced, radiation-induced inflammation and fibrosis</td>
</tr>
<tr>
<td>Visceral larva migrans</td>
<td>Neoplasms and neoplastic-like conditions</td>
</tr>
<tr>
<td>Inadequately treated bacterial infection</td>
<td>Primary or metastatic pulmonary tumors</td>
</tr>
<tr>
<td>Interstitial pneumonitis and fibrosis</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Usual interstitial pneumonitis</td>
<td>Histiocytosis</td>
</tr>
<tr>
<td>Lymphoid (AIDS)</td>
<td>Eosinophilic pneumonias</td>
</tr>
<tr>
<td>Genetic disorders of surfactant synthesis, secretion</td>
<td>Other etiologies</td>
</tr>
<tr>
<td>Desquamative</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Acute (Hamman-Rich)</td>
<td>Congenital</td>
</tr>
<tr>
<td>Alveolar proteinosis</td>
<td>Postinfectious</td>
</tr>
<tr>
<td>Drug-induced, radiation-induced inflammation and fibrosis</td>
<td>Sarcoidosis</td>
</tr>
</tbody>
</table>

**RECURRENT AND PERSISTENT LUNG INFLTRATES**

Radiographic lung infiltrates resulting from acute pneumonia usually resolve within 1-3 wk, but a substantial number of children, particularly infants, fail to completely clear infiltrates within a 4 wk period. These children may be febrile or alebrile and may display a wide range of respiratory symptoms and signs. Persistent or recurring infiltrates present a diagnostic challenge (Table 384-6).

Symptoms associated with chronic lung infiltrates in the 1st several weeks of life (but not related to neonatal respiratory distress syndrome) suggest infection acquired in utero or during descent through the birth canal. Early appearance of chronic infiltrates can also be associated with cystic fibrosis or congenital anomalies that result in aspiration or...
airway obstruction. A history of recurrent infiltrates, wheezing, and cough may reflect asthma, even in the 1st yr of life.

A controversial association has been posed regarding recurrent lung infiltrates in pulmonary hemosiderosis related to cow’s milk hypersensitivity or unknown causes appearing in the 1st yr of life. Children with a history of bronchopulmonary dysplasia often have episodes of respiratory distress attended by wheezing and new lung infiltrates. Recurrent pneumonia in a child with frequent otitis media, nasopharyngitis, adenitis, or dermatologic manifestations suggests an immunodeficiency state, complement deficiency, or phagocytic defect (see Chapters 124-127). Primary ciliary dyskinesia is also of consideration in patients with frequent otitis media and suppurative sinopulmonary disease, with or without accompanying heterotaxy or infertility. Pulmonary sequestration may be suspected in patients with recurrent findings on radiograph that occur in the same location, both during illness and when well (see Chapter 395.4). Traction bronchiectasis may also be suggested on radiography with persistent findings in a given region of the film following history of respiratory infection. Particular attention must be directed to the possibility that the infiltrates represent lymphocytic interstitial pneumonitis or opportunistic infection associated with HIV infection (see Chapter 276). A history of paroxysmal coughing in an infant suggests pertussis syndrome or cystic fibrosis. Persistent infiltrates, especially with loss of volume, in a toddler should suggest foreign-body aspiration.

Overinflation and infiltrates suggest cystic fibrosis or chronic asthma. A “silent chest” with infiltrates should arouse suspicion of alveolar proteinosis (see Chapter 405), Pneumocystis jiroveci infection (see Chapter 244), genetic disorders of surfactant synthesis and secretion causing interstitial pneumonitis, or tumors. Growth should be carefully assessed to determine whether the lung process has had systemic effects, indicating substantial severity and chronicity as in cystic fibrosis or alveolar proteinosis. Cataracts, retinopathy, or microcephaly suggest in utero infection. Chronic rhinorrhea can be associated with atopic disease, cow's milk intolerance, cystic fibrosis, or congenital syphilis. The absence of tonsils and cervical lymph nodes suggests an immunodeficiency state.

Diagnostic studies should be performed selectively, based on information obtained from history and physical examination and on a thorough understanding of the conditions listed in Table 384-6. Cytologic evaluation of sputum, if available, may be helpful. Chest CT often provides more precise anatomic detail concerning the infiltrate or further characterize a region of anatomic abnormality. Bronchoscopy is indicated for detecting foreign bodies, congenital or acquired anomalies of the tracheobronchial tract, and obstruction by endobronchial or extrinsic masses (see Chapter 394). Bronchoscopy provides access to secretions that can be studied cytologically and microbiologically. Alveolar lavage fluid is diagnostic for alveolar proteinosis and persistent pulmonary hemosiderosis and can suggest aspiration syndromes. If all appropriate studies have been completed and the condition remains undiagnosed, lung biopsy might yield a definitive diagnosis, such as in interstitial lung disease or in fungal disease.

Optimal medical or surgical treatment of chronic lung infiltrates often depends on a specific diagnosis, but chronic conditions may be self-limiting (severe and prolonged viral infections in infants); in these cases, symptomatic therapy can maintain adequate lung function until spontaneous improvement occurs. Helpful measures include inhalation and physical therapy for excessive secretions, antibiotics for bacterial infections, supplementary oxygen for hypoxemia, and maintenance of adequate nutrition. Because the lung of a young child has remarkable recuperative potential, normal lung function may ultimately be achieved with treatment despite the severity of pulmonary insult occurring in infancy or early childhood.

Bibliography is available at Expert Consult.
Bibliography


Chapter 385

Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis)

Genie E. Roosevelt

Airway resistance is inversely proportional to the 4th power of the radius (see Chapter 373). Because the lumen of an infant's or child's airway is narrow, minor reductions in cross-sectional area as a result of mucosal edema or other inflammatory processes cause an exponential increase in airway resistance and a significant increase in the work of breathing. The larynx is composed of 4 major cartilages (epiglottic, arytenoid, thyroid, and cricoid cartilages, ordered from superior to inferior) and the soft tissues that surround them. The cricoid cartilage encircles the airway just below the vocal cords and defines the narrowest portion of the upper airway in children younger than 10 yr of age.

Inflammation involving the vocal cords and structures inferior to the cords is called laryngitis, laryngotracheitis, or laryngotracheo-bronchitis, and inflammation of the structures superior to the cords (i.e., arytenoids, aryepiglottic folds ["false cords"], epiglottis) is called supraglottitis. The term croup refers to a heterogeneous group of mainly acute and infectious processes that are characterized by a bark-like or brassy cough and may be associated with hoarseness, inspiratory stridor, and respiratory distress. Stridor is a harsh, high-pitched respiratory sound, which is usually inspiratory but can be biphasic and is produced by turbulent airflow; it is not a diagnosis but a sign of upper airway obstruction (see Chapter 374). Croup typically affects the larynx, trachea, and bronchi. When the involvement of the larynx is sufficient to produce symptoms, they dominate the clinical picture over the tracheal and bronchial signs. A distinction has been made between spasmodic or recurrent croup and laryngotracheobronchitis. Some clinicians believe that spasmodic croup might have an allergic component and improves rapidly without treatment, whereas laryngotracheobronchitis is always associated with a viral infection of the respiratory tract. Others believe that the signs and symptoms are similar enough to consider them within the spectrum of a single disease, in part because studies have documented viral etiologies in both acute and recurrent croup.

385.1 Infectious Upper Airway Obstruction

Genie E. Roosevelt

ETIOLOGY AND EPIDEMIOLOGY

With the exceptions of diphtheria (see Chapter 187), bacterial tracheitis, and epiglottitis, most acute infections of the upper airway are caused by viruses. The parainfluenza viruses (types 1, 2, and 3; see Chapter 259) account for approximately 75% of cases; other viruses
associated with croup include influenza A and B, adenovirus, respiratory syncytial virus, and measles. Influenza A is associated with severe laryngotracheobronchitis. *Mycoplasma pneumoniae* has rarely been isolated from children with croup and causes mild disease (see Chapter 223). Most patients with croup are between the ages of 3 mo and 5 yr, with the peak in the 2nd yr of life. The incidence of croup is higher in boys. It occurs most commonly in the late fall and winter but can occur throughout the year. Recurrences are frequent from 3-6 yr of age and decrease with growth of the airway. Approximately 15% of patients have a strong family history of croup.

In the past, *Haemophilus influenzae* type b was the most commonly identified etiology of acute epiglottitis. Since the widespread use of the *H. influenzae* type b vaccine, invasive disease caused by *H. influenzae* type b in pediatric patients has been reduced by 99% (see Chapter 194). Therefore, other agents, such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, nontypeable *H. influenzae*, and *Staphylococcus aureus*, represent a larger portion of pediatric cases of epiglottitis in vaccinated children. In the prevaccine era, the typical patient with epiglottitis caused by *H. influenzae* type b was 2-4 yr of age, although cases were seen in the 1st yr of life and in patients as old as 7 yr of age. Currently, the most common presentation of epiglottitis is an adult with a sore throat, although cases still do occur in underimmunized children; vaccine failures have been reported.

**CLINICAL MANIFESTATIONS**

**Croup (Laryngotracheobronchitis)**

Viruses typically cause croup, the most common form of acute upper respiratory obstruction. The term *laryngotracheobronchitis* refers to viral infection of the glottic and subglottic regions. Some clinicians use the term *laryngotracheitis* for the most common and most typical form of croup and reserve the term *laryngotracheobronchitis* for the more severe form that is considered an extension of laryngotracheitis associated with bacterial superinfection that occurs 5-7 days into the clinical course.

Most patients have an upper respiratory tract infection with some combination of rhinorrhea, pharyngitis, mild cough, and low-grade fever for 1-3 days before the signs and symptoms of upper airway obstruction become apparent. The child then develops the characteristic “barking” cough, hoarseness, and inspiratory stridor. The low-grade fever can persist, although temperatures may occasionally reach 39-40°C (102.2-104°F); some children are afebrile. Symptoms are characteristically worse at night and often recur with decreasing intensity for several days and resolve completely within a week. Agitation and crying greatly aggravate the symptoms and signs. The child may prefer to sit up in bed or be held upright. Older children usually are not seriously ill. Other family members might have mild respiratory illnesses with laryngitis. Most young patients with croup progress only as far as the other supraglottic structures, especially the aryepiglottic folds, are more involved than the epiglottis itself. In a patient in whom the diagnosis is certain or probable based on clinical grounds, laryngoscopy should always take priority.

Physical examination can reveal a hoarse voice, coryza, normal to moderately inflamed pharynx, and a slightly increased respiratory rate. Patients vary substantially in their degrees of respiratory distress. Rarely, the upper airway obstruction progresses and is accompanied by an increasing respiratory rate; nasal flaring; suprasternal, infraternal, and intercostal retractions; and continuous stridor. Croup is a disease of the upper airway, and alveolar gas exchange is usually normal. Hypoxia and low oxygen saturation are seen only when complete airway obstruction is imminent. The child who is hypoxic, cyanotic, pale, or obtunded needs immediate airway management.

Occasionally, the pattern of severe laryngotracheobronchitis is difficult to differentiate from epiglottitis, despite the usually more acute onset and rapid course of the latter.

Croup is a clinical diagnosis and does not require a radiograph of the neck. Radiographs of the neck can show the typical subglottic narrowing, or steeple sign, of croup on the posteroanterior view (Fig. 385-1). However, the steeple sign may be absent in patients with croup, may be present in patients without croup as a normal variant, and may rarely be present in patients with epiglottitis. The radiographs do not correlate well with disease severity. Radiographs should be considered only after airway stabilization in children who have an atypical presentation or clinical course. Radiographs may be helpful in distinguishing between severe laryngotracheobronchitis and epiglottitis, but airway management should always take priority.

**Acute Epiglottitis (Supraglottitis)**

This now rare, but still dramatic and potentially lethal condition is characterized by an acute rapidly progressive and potentially fulminating course of high fever, sore throat, dyspnea, and rapidly progressing respiratory obstruction. The degree of respiratory distress at presentation is variable. The initial lack of respiratory distress can deceive the unwary clinician; respiratory distress can also be the first manifestation. Often, the otherwise healthy child suddenly develops a sore throat and fever. Within a matter of hours, the patient appears toxic, swallowing is difficult, and breathing is labored. Drooling is usually present and the neck is hyperextended in an attempt to maintain the airway. The child may assume the tripod position, sitting upright and leaning forward with the chin up and mouth open while bracing on the arms. A brief period of air hunger with restlessness may be followed by rapidly increasing cyanosis and coma. Stridor is a late finding and suggests near-complete airway obstruction. Complete obstruction of the airway and death can ensue unless adequate treatment is provided. The barking cough typical of croup is rare. Usually, no other family members are ill with acute respiratory symptoms.

The diagnosis requires visualization under controlled circumstances of a large, cherry red, swollen epiglottis by laryngoscopy. Occasionally, the other supraglottic structures, especially the aryepiglottic folds, are more involved than the epiglottis itself. In a patient in whom the diagnosis is certain or probable based on clinical grounds, laryngoscopy should be performed expeditiously in a controlled environment such as an operating room or intensive care unit. Anxiety-provoking interventions such as phlebotomy, intravenous line placement, placing the child supine, or direct inspection of the oral cavity should be avoided until the airway is secure. If epiglottitis is thought to be possible but not certain in a patient with acute upper airway obstruction, the patient may undergo lateral radiographs of the upper airway first. Classic radiographs of a child who has epiglottitis show the thumb sign (Fig. 385-2). Proper positioning of the patient for the lateral neck radiograph is crucial in order to avoid some of the pitfalls associated with interpretation of the film. Adequate hyperextension of the head and neck is necessary. In addition, the epiglottis can appear to be round if the lateral neck is taken at an oblique angle. If the concern for epiglottitis still exists after the radiographs, direct visualization should be performed. A physician skilled in airway management and use of
Acute Infectious Laryngitis

Laryngitis is a common illness. Viruses cause most cases; diphtheria is an exception but is extremely rare in industrialized countries (see Chapter 187). The onset is usually characterized by an upper respiratory tract infection during which sore throat, cough, and hoarseness appear. The illness is generally mild; respiratory distress is unusual except in the young infant. Hoarseness and loss of voice may be out of proportion to systemic signs and symptoms. The physical examination is usually not remarkable except for evidence of pharyngeal inflammation. Inflammatory edema of the vocal cords and subglottic tissue may be demonstrated laryngoscopically. The principal site of obstruction is usually the subglottic area.

Spasmodic Croup

Spasmodic croup occurs most often in children 1-3 yr of age and is clinically similar to acute laryngotracheobronchitis, except that the history of a viral prodrome and fever in the patient and family are often absent. The cause is viral in some cases, but allergic and psychologic factors may be important in others.

Occurring most commonly in the evening or nighttime, spasmodic croup begins with a sudden onset that may be preceded by mild to moderate coryza and hoarseness. The child awakens with a characteristic barking, metallic cough, noisy inspiration, and respiratory distress and appears anxious and frightened. The patient is usually afebrile. The severity of the symptoms generally diminishes within several hr, and the following day, the patient often appears well except for slight hoarseness and cough. Similar, but usually less severe, attacks without extreme respiratory distress can occur for another night or two. Such episodes often recur several times. Spasmodic croup might represent more of an allergic reaction to viral antigens than direct infection, although the pathogenesis is unknown.

DIFFERENTIAL DIAGNOSIS

These 4 syndromes must be differentiated from one another and from a variety of other entities that can present as upper airway obstruction. Bacterial tracheitis is the most important differential diagnostic consideration and has a high risk of airway obstruction. Diphtheretic croup is extremely rare in North America, although a major epidemic of diphtheria occurred in countries of the former Soviet Union beginning in 1990 from the lack of routine immunization. Early symptoms of diphtheria include malaise, sore throat, anorexia, and low-grade fever. Within 2-3 days, pharyngeal examination reveals the typical gray-white membrane, which can vary in size from covering a small patch on the tonsils to covering most of the soft palate. The membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding. The course is usually insidious, but respiratory obstruction can occur suddenly. Measles croup almost always coincides with the full manifestations of systemic disease and the course may be fulminant (see Chapter 246).

Sudden onset of respiratory obstruction can be caused by aspiration of a foreign body (see Chapter 387). The child is usually 6 mo-3 yr of age. Choking and coughing occur suddenly, usually without prodromal signs of infection, although children with a viral infection can also aspirate a foreign body. A retropharyngeal or peritonsillar abscess can mimic respiratory obstruction (see Chapter 382). CT scans of the upper airway are helpful in evaluating the possibility of a retropharyngeal abscess. A peritonsillar abscess is a clinical diagnosis. Other possible causes of upper airway obstruction include extrinsic compression of the airway (laryngeal web, vascular ring) and intraluminal obstruction from masses (laryngeal papilloma, subglottic hemangioma); these tend to have chronic or recurrent symptoms.

Upper airway obstruction is occasionally associated with angioedema of the subglottic areas as part of anaphylaxis and generalized allergic reactions, edema after endotracheal intubation for general anesthesia or respiratory failure, hypocalcemic tetany, infectious mononucleosis, trauma, and tumors or malformations of the larynx. A croupy cough may be an early sign of asthma. Vocal cord dysfunction can also occur. Epiglottitis, with the characteristic manifestations of drooling or dysphagia and stridor, can also result from the accidental ingestion of very hot liquid.

COMPLICATIONS

Complications occur in approximately 15% of patients with viral croup. The most common is extension of the infectious process to involve other regions of the respiratory tract, such as the middle ear, the terminal bronchioles, or the pulmonary parenchyma. Bacterial tracheitis may be a complication of viral croup rather than a distinct disease. If associated with S. aureus or S. pyogenes, toxic shock syndrome can develop. Bacterial tracheitis may have a 2-phased illness, with the 2nd phase after a croup-like illness associated with high fever, toxicity, and airway obstruction. Alternatively, the onset of tracheitis occurs without a 2nd phase and appears as a continuation of the initial croup-like illness but with higher fever and worsening respiratory distress rather than the usual recovery after 2-3 days of viral croup. Pneumonia, cervical lymphadenitis, otitis media, or, rarely, meningitis or septic arthritis can occur in the course of epiglottitis. Pneumomediastinum and pneumothorax are the most common complications of tracheotomy.

TREATMENT

The mainstay of treatment for children with croup is airway management and treatment of hypoxia. Treatment of the respiratory distress
should take priority over any testing. Most children with either acute spasmodic croup or infectious croup can be managed safely at home. Despite the observation that cold night air is beneficial, a Cochrane review has found no evidence supporting the use of cool mist in the emergency department for the treatment of croup.

**Nebulized racemic epinephrine** is an accepted treatment for moderate or severe croup. The mechanism of action is believed to be constriction of the precapillary arterioles through the β-adrenergic receptors, causing fluid resorption from the interstitial space and a decrease in the laryngeal mucosal edema.Traditionally, racemic epinephrine, a 1:1 mixture of the D- and L-isomers of epinephrine, has been administered. A dose of 0.25-0.5 mL of 2.25% racemic epinephrine in 3 mL of normal saline can be used as often as every 20 min. Racemic epinephrine was initially chosen over the more active and more readily available L-epinephrine to minimize anticipated cardiovascular side effects such as tachycardia and hypertension. There is evidence that L-epinephrine (5 mL of 1:1,000 solution) is equally effective as racemic epinephrine and does not carry the risk of additional adverse effects.

The indications for the administration of nebulized epinephrine include moderate to severe stridor at rest, the possible need for intubation, respiratory distress, and hypoxia. The duration of activity of racemic epinephrine is <2 hr. Consequently, observation is mandated. The symptoms of croup might reappear, but racemic epinephrine does not cause rebound worsening of the obstruction. Patients can be safely discharged home after a 2-3 hr period of observation provided they have no stridor at rest; have normal air entry, normal pulse oximetry, and normal level of consciousness; and have received steroids. Nebulized epinephrine should still be used cautiously in patients with tachycardia, heart conditions such as tetralogy of Fallot, or ventricular outlet obstruction because of possible side effects.

The effectiveness of **oral corticosteroids** in viral croup is well established. Corticosteroids decrease the edema in the laryngeal mucosa through their anti-inflammatory action. Oral steroids are beneficial, even in mild croup, as measured by reduced hospitalization, shorter duration of hospitalization, and reduced need for subsequent interventions such as epinephrine administration. Most studies that demonstrated the efficacy of oral dexamethasone used a single dose of 0.6 mg/kg, a dose as low as 0.15 mg/kg may be just as effective. Intramuscular dexamethasone and nebulized budesonide have an equivalent clinical effect; oral dosing of dexamethasone is as effective as intramuscular administration. A single dose of oral prednisolone is less effective. There are no controlled studies examining the effectiveness of multiple doses of corticosteroids. The only adverse effect in the treatment of croup with corticosteroids is the development of *Candida albicans* laryngotracheitis in a patient who received dexamethasone, 1 mg/kg/24 hr for 8 days. Corticosteroids should not be administered to children with varicella or tuberculosis (unless the patient is receiving appropriate antituberculosis therapy) because they worsen the clinical course.

Antibiotics are not indicated in croup. Nonprescription cough and cold medications should not be used in children younger than 4 yr of age. A helium-oxygen mixture (heliox) may be considered in the treatment of children with severe croup for whom intubation is being considered although the evidence is inconclusive. Children with croup should be hospitalized for any of the following: progressive stridor, severe stridor at rest, respiratory distress, hypoxia, cyanosis, depressed mental status, poor oral intake, or the need for reliable observation. **Epiglottitis** is a medical emergency and warrants immediate treatment with an **artificial airway** placed under controlled conditions, either in an operating room or intensive care unit. All patients should receive oxygen en route unless the mask causes excessive agitation. Racemic epinephrine and corticosteroids are ineffective. Cultures of blood, epiglottic surface, and, in selected cases, cerebrospinal fluid should be collected after the airway is stabilized. **Cefotaxime**, **ceftriaxone**, or **meropenem** should be given parenterally, pending culture and susceptibility reports, because 10-40% of *H. influenzae* type b cases are resistant to ampicillin. After insertion of the artificial airway, the patient should improve immediately, and respiratory distress and cyanosis should disappear. Epiglottitis resolves after a few days of antibiotics, and the patient may be extubated; antibiotics should be continued for at least 10 days. Chemoprophylaxis is not routinely recommended for household, childcare, or nursery contacts of patients with invasive *H. influenzae* type b infections, but careful observation is mandatory, with prompt medical evaluation when exposed children develop a febrile illness. **Indications for rifampin prophylaxis** (20 mg/kg orally once a day for 4 days; maximum dose: 600 mg) for all household members include a child within the home who is younger than 4 yr of age and incompletely immunized, younger than 12 mo of age and has not completed the primary vaccination series, or immunocompromised.

**Acute laryngeal swelling on an allergic basis** responds to epinephrine (1:1,000 dilution in dosage of 0.01 mL/kg to a maximum of 0.5 mL/dose) administered intramuscularly or racemic epinephrine (dose of 0.5 mL of 2.25% racemic epinephrine in 3 mL of normal saline) (see Chapter 149). Corticosteroids are often required (1-2 mg/kg/24 hr of prednisone for 3-5 days). After recovery, the patient and parents should be discharged with a preloaded syringe of epinephrine to be used in emergencies. Reactive mucosal swelling, severe stridor, and respiratory distress unresponsive to mist therapy may follow endotracheal intubation for general anesthesia in children. Racemic epinephrine and corticosteroids are helpful.

**Endotracheal/Nasotracheal Intubation and Tracheotomy**

With the introduction of routine intubation or, less often, tracheotomy for epiglottitis, the mortality rate for epiglottis has dropped to almost zero. These procedures should always be performed in an operating room or intensive care unit if time permits; prior intubation and general anesthesia greatly facilitate performing a tracheotomy without complications. The use of an endotracheal or nasotracheal tube that is 0.5-1.0 mm smaller than estimated by age or height is recommended to facilitate intubation and reduce long-term sequelae. The choice of procedure should be based on the local expertise and experience with the procedure and postoperative care.

Intubation or tracheotomy is required for most patients with bacterial tracheitis and all young patients with epiglitis. It is rarely required for patients with laryngotracheobronchitis, spasmodic croup, or laryngitis. Severe forms of laryngotracheobronchitis that require intubation in a high proportion of patients have been reported during severe measles and influenza A virus epidemics. Assessing the need for these procedures requires experience and judgment because they should not be delayed until cyanosis and extreme restlessness have developed (see Chapter 71). As with epiglottitis, an endotracheal or nasotracheal tube that is 0.5-1.0 mm smaller than estimated by age or height is recommended.

The endotracheal tube or tracheotomy must remain in place until edema and spasm have subsided and the patient is able to handle secretions satisfactorily. It should be removed as soon as possible, usually within a few days. Adequate resolution of epiglottic inflammation that has been accurately confirmed by fiberoptic laryngoscopy, permitting much more rapid extubation, often occurs within 24 hr. Racemic epinephrine and dexamethasone (0.5 mg/kg/dose 6-12 hr prior to extubation then every 6 hr for 6 doses with a maximum dose of 10 mg) may be useful in the treatment of upper airway edema seen postintubation.

**PROGNOSIS**

In general, the length of hospitalization and the mortality rate for cases of acute infectious upper airway obstruction increase as the infection extends to involve a greater portion of the respiratory tract, except in epiglottitis, in which the localized infection itself can prove to be fatal. Most deaths from croup are caused by a laryngeal obstruction or by the complications of tracheotomy. Rarely, fatal out-of-hospital arrests caused by viral laryngotracheobronchitis have been reported, particularly in infants and in patients whose course has been complicated by bacterial tracheitis. Untreated epiglottitis has a mortality rate of 6% in some series, but if the diagnosis is made and appropriate treatment is initiated before the patient is moribund, the prognosis is excellent. The...
outcome of acute laryngotracheobronchitis, laryngitis, and spasmodic croup is also excellent.

Bibliography is available at Expert Consult.

385.2 Bacterial Tracheitis

Genie E. Roosevelt

Bacterial tracheitis is an acute bacterial infection of the upper airway that is potentially life threatening. *S. aureus* (see Chapter 181) is the most commonly isolated pathogen with isolated reports of methicillin-resistant *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *Moraxella catarrhalis*, nontypeable *H. influenzae*, and anaerobic organisms have also been implicated. The mean age is between 5 and 7 yr. There is a slight male predominance. Bacterial tracheitis often follows a viral respiratory infection (especially laryngotracheitis), so it may be considered a bacterial complication of a viral disease, rather than a primary bacterial illness. This life-threatening entity is more common than epiglottitis in vaccinated populations.

**CLINICAL MANIFESTATIONS**

Typically, the child has a brassy cough, apparently as part of a viral laryngotracheobronchitis. High fever and “toxicity” with respiratory distress can occur immediately or after a few days of apparent improvement. The patient can lie flat, does not drool, and does not have the dysphagia associated with epiglottitis. The usual treatment for croup (racemic epinephrine) is ineffective. Intubation or tracheostomy may be necessary, but only 50-60% of patients require intubation for management; younger patients are more likely to need intubation. The major pathologic feature appears to be mucosal swelling at the level of the cricoid cartilage, complicated by copious, thick, purulent secretions, sometimes causing pseudomembranes. Suctioning these secretions, although occasionally affording temporary relief, usually does not sufficiently obviate the need for an artificial airway.

**DIAGNOSIS**

The diagnosis is based on evidence of bacterial upper airway disease, which includes high fever, purulent airway secretions, and an absence of the classic findings of epiglottitis. X-rays are not needed but can show the classic findings (Fig. 385-3); purulent material is noted below the cords during endotracheal intubation (Fig. 385-4).

**TREATMENT**

Appropriate antimicrobial therapy, which usually includes antistaphylococcal agents, should be instituted in any patient whose course suggests bacterial tracheitis. Current empiric therapy recommendations for bacterial tracheitis include vancomycin or clindamycin and a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone). When bacterial tracheitis is diagnosed by direct laryngoscopy or is strongly
Bibliography

Laryngotracheobronchitis


Epiglottitis

suspected on clinical grounds, an artificial airway should be strongly considered. Supplemental oxygen is usually necessary.

**COMPLICATIONS**

Chest radiographs often show patchy infiltrates and may show focal densities. Subglottic narrowing and a rough and ragged tracheal air column can often be demonstrated radiographically. If airway management is not optimal, cardiorespiratory arrest can occur. Toxic shock syndrome has been associated with staphylococcal and group A streptococcal tracheitis (see Chapter 181.2).

**PROGNOSIS**

The prognosis for most patients is excellent. Patients usually become afebrile within 2-3 days of the institution of appropriate antimicrobial therapy, but prolonged hospitalization may be necessary. In recent years, there appears to be a trend toward a less-morbid condition. With a decrease in mucosal edema and purulent secretions, extubation can be accomplished safely, and the patient should be observed carefully while antibiotics and oxygen therapy are continued.

*Bibliography is available at Expert Consult.*
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The larynx functions as a breathing passage, a valve to protect the lungs, and the primary organ of communication; symptoms of laryngeal anomalies are those of airway obstruction, difficulty feeding, and abnormalities of phonation (see Chapter 373). Obstructive congenital lesions of the upper airway produce turbulent airflow according to the laws of fluid dynamics. This rapid, turbulent airflow across a narrowed segment of respiratory tract produces distinctive sounds that are diagnostically useful to the clinician. The timing of noisy breathing in relation to the sleep–wake cycle is important. Obstruction of the pharyngeal airway (by enlarged tonsils, adenoids, tongue, or syndromes with midface hypoplasia) typically produces worse obstruction during sleep than during waking. Obstruction that is worse when awake is typically laryngeal, tracheal, or bronchial, and is exacerbated by exertion. The location of the obstruction dictates the respiratory phase, tone and nature of the sound and these qualities direct the differential diagnosis. Intrathoracic lesions typically cause expiratory wheezing and stridor, often masquerading as asthma. The expiratory wheezing contrasts to the inspiratory stridor caused by the extrathoracic lesions of congenital laryngeal anomalies, specifically laryngomalacia and bilateral vocal cord paralysis. Stridor describes the low-pitched inspiratory snoring sound typically produced by nasal or nasopharyngeal obstruction.

With airway obstruction, the severity of the obstructing lesion, the work of breathing, determines the necessity for diagnostic procedures and surgical intervention. Obstructive symptoms vary from mild to severe stridor with episodes of apnea, cyanosis, suprasternal (tracheal tugging) and substernal retractions, dyspnea, and tachypnea. Congenital anomalies of the trachea and bronchi can create serious respiratory difficulties from the 1st few min of life. Chronic obstruction can cause failure to thrive.

Bibliography is available at Expert Consult.

386.1 Laryngomalacia
James W. Schroeder Jr. and Lauren D. Holinger

CLINICAL MANIFESTATIONS
Laryngomalacia is the most common congenital laryngeal anomaly and the most common cause of stridor in infants and children. Sixty percent of congenital laryngeal anomalies in children with stridor are due to laryngomalacia. Stridor is inspiratory, low-pitched, and exacerbated by any exertion: crying, agitation, or feeding. The stridor is caused, in part, by decreased laryngeal tone leading to supraglottic collapse during inspiration. Symptoms usually appear within the 1st 2 wk of life and increase in severity for up to 6 mo, although gradual improvement can begin at any time. Gastroesophageal reflux disease and neurologic disease influence the severity of the disease and thereby the clinical course.

DIAGNOSIS
The diagnosis is made primarily based on symptoms. The diagnosis is confirmed by outpatient flexible laryngoscopy (Fig. 386-1). When the work of breathing is moderate to severe, airway films and chest radiographs are indicated. Laryngomalacia can contribute to feeding difficulties and dysphagia in some children because of decreased laryngeal sensation and poor suck swallow breath coordination. When the inspiratory stridor sounds wet or is associated with a cough or when there is a history of repeat upper respiratory illness or pneumonia, dysphagia should be considered. When dysphagia is suspected, a contrast swallow study and/or a fiberoptic endoscopic evaluation of swallowing esophagram may be considered. Because 15-60% of infants with laryngomalacia have synchronous airway anomalies, complete bronchoscopy is undertaken for patients with moderate to severe obstruction.

TREATMENT
Expectant observation is suitable for most infants because most symptoms resolve spontaneously as the child and airway grow.

Figure 386-1 Endoscopic example of laryngomalacia. On inspiration, the epiglottic folds collapse into the airway. The lateral tips of the epiglottis are also collapsing inward (arrow). (From Slovis TL, editor: Caffey’s pediatric diagnostic imaging, ed 11. Philadelphia, 2008, Mosby.)
Bibliography

Laryngopharyngeal reflux is managed aggressively. In 15-20% of patients symptoms are severe enough to cause progressive respiratory distress, cyanosis, or failure to thrive. In these patients surgical intervention via supraglottoplasty is considered. Supraglottoplasty is 90% successful in relieving upper airway obstruction caused by laryngomalacia.

Bibliography is available at Expert Consult.

### 386.2 Congenital Subglottic Stenosis

**James W. Schroeder Jr. and Lauren D. Holinger**

**CLINICAL MANIFESTATIONS**

Congenital subglottic stenosis is the second most common cause of stridor. The subglottis is the narrowest part of the upper airway in a child. Subglottic stenosis is a narrowing of the subglottic larynx, which is the space extending from the undersurface of the true vocal cords to the inferior margin of the cricoid cartilage. It typically causes respiratory distress and biphasic or primarily inspiratory stridor. It may be congenital or acquired. Symptoms often occur with a respiratory tract infection as the edema and thickened secretions of the common cold narrow an already compromised airway leading to recurrent or persistent croup like symptoms.

Biphasic or primarily inspiratory stridor is the typical presenting symptom for congenital subglottic stenosis. Recurrent or persistent croup usually occurs in these children at 6 mo of age or younger. The edema and thickened secretions of the common cold further narrow an already marginal airway that leads to croup-like symptoms. The stenosis can be caused by an abnormally shaped cricoid cartilage; by a tracheal ring that becomes trapped underneath the cricoid cartilage; or by soft tissue thickening caused by ductal cysts, submucosal gland hyperplasia or fibrosis.

**DIAGNOSIS**

The diagnosis made by airway radiographs is confirmed by direct laryngoscopy. During diagnostic laryngoscopy the subglottic larynx is visualized directly and sized objectively using endotracheal tubes (Fig. 386-2). The percentage of stenosis is determined by comparing the size of the patients’ larynx to a standard of laryngeal dimensions based on age. Stenosis >50% is usually symptomatic and often requires treatment. As with all cases of upper airway obstruction, tracheostomy is avoided when possible. Dilation and endoscopic laser surgery are rarely effective because most congenital stenoses are cartilaginous. Anterior laryngotracheal decompression (cricoid split) or laryngotracheal reconstruction with cartilage grafting is usually effective in avoiding tracheostomy. The differential diagnosis includes other anatomic anomalies as well as a hemangioma or papillomatosis.

Bibliography is available at Expert Consult.

### 386.3 Vocal Cord Paralysis

**James W. Schroeder Jr. and Lauren D. Holinger**

**CLINICAL MANIFESTATIONS**

Vocal cord paralysis is the third most common congenital laryngeal anomaly that produces stridor in infants and children. Congenital central nervous system lesions such as myelomeningocele, Chiari malformation, and hydrocephalus may be associated with bilateral paralysis.

Unilateral vocal cord paralysis is most often iatrogenic as a result of surgical treatment for gastrointestinal (tracheoesophageal fistula) and cardiovascular (patent ductus arteriosis repair) anomalies. Bilateral vocal cord paralysis produces airway obstruction manifested by high-pitched inspiratory stridor: a phonatory sound or inspiratory cry. Unilateral paralysis causes aspiration, coughing, and choking; the cry is weak and breathy, but stridor and other symptoms of airway obstruction are less common.

**DIAGNOSIS**

The diagnosis of vocal cord paralysis is made by awake flexible laryngoscopy. A thorough investigation for the underlying primary cause is indicated. Because of the association with other congenital lesions, evaluation includes neurology and cardiology consultations as well as diagnostic endoscopy of the larynx, trachea, and bronchi.

**TREATMENT**

Treatment is based on the severity of the symptoms. Vocal cord paralysis in infants usually resolves spontaneously within 6-12 mo. If it does not resolve within 2-3 yr, it is unlikely to do so. Bilateral paralysis can require temporary tracheotomy. Procedures that widen the posterior glottis to relieve the obstruction include laryngotracheal reconstruction using an endoscopically placed posterior glottis cartilage graft, or arytenoidectomy, or arytenoid lateralization. These procedures are successful in reducing the obstruction. However, they may result in aspiration that may become severe. For unilateral vocal cord paralysis with aspiration, injection laterally to the paralyzed vocal cord moves it medially to reduce aspiration and related complications.

### 386.4 Congenital Laryngeal Webs and Atresia

**James W. Schroeder Jr. and Lauren D. Holinger**

Most congenital laryngeal webs are glottic with subglottic extension and associated subglottic stenosis. Chromosomal and cardiovascular anomalies as well as chromosome 22 q 11 deletion are common in patients with congenital laryngeal web. Airway obstruction is not always present and may be related to the subglottic stenosis. Thick webs may be suspected in lateral radiographs of the airway. Diagnosis is made by direct laryngoscopy (Fig. 386-3). Treatment might require only incision or dilation. Webs with associated subglottic stenosis are likely to require cartilage augmentation of the cricoid cartilage (laryngotracheal reconstruction). Laryngeal atresia occurs as a complete glottic web and commonly is associated with tracheal agenesis and tracheoesophageal fistula.

Bibliography is available at Expert Consult.
Bibliography
Bibliography

Bibliography
386.5 Congenital Subglottic Hemangioma  
James W. Schroeder Jr. and Lauren D. Holinger

Symptoms of airway obstruction typically occur within the 1st 2 mo. of life. Stridor is biphasic but usually more prominent during inspiration. A barking cough, hoarseness, and symptoms of recurrent or persistent croup are typical. Only 1% of children who have cutaneous hemangiomas will have a subglottic hemangioma. However, 50% of those with a subglottic hemangioma will have a cutaneous hemangioma. A facial hemangioma is not always present, but when it is evident, it is in the beard distribution. Chest and neck radiographs can show the characteristic asymmetric narrowing of the subglottic larynx. Treatment is discussed in Chapter 390.3.

Bibliography is available at Expert Consult.

386.6 Laryngoceles and Saccular Cysts  
James W. Schroeder Jr. and Lauren D. Holinger

A laryngocele is an abnormal air-filled dilation of the laryngeal saccula that arises vertically between the vocal cords and the false vocal cord. It communicates with the laryngeal lumen and, when intermittently filled with air, causes hoarseness and dyspnea. A saccular cyst (congenital cyst of the larynx) is distinguished from the laryngocele in that its lumen is isolated from the interior of the larynx and it contains mucus, not air in infants and children. Laryngoceles cause hoarseness and dyspnea that may increase with crying. Saccular cysts may cause respiratory distress and stridor. A saccular cyst may be visible on radiography, but the diagnosis is made by laryngoscopy (Fig. 386-4). Needle aspiration of the cyst confirms the diagnosis but rarely provides a cure. Approaches include endoscopic CO₂ laser excision, endoscopic extended ventriculoloty (marsupialization or unroofing), or, traditionally, external excision.

Bibliography is available at Expert Consult.

386.7 Posterior Laryngeal Cleft and Laryngotracheoesophageal Cleft  
James W. Schroeder Jr. and Lauren D. Holinger

The posterior laryngeal cleft is characterized by aspiration and is the result of a deficiency in the midline of the posterior larynx. Posterior laryngeal clefts are categorized into 4 types. Type 1 clefts are mild and the interarytenoid notch only extends down to the level of the true vocal cords; 60% of these will cause no symptoms and will not require surgical repair. In severe cases, the cleft (type 4) extends inferiorly into the cervical or thoracic trachea so there is no separation between the trachea and esophagus, creating a laryngotracheoesophageal cleft. Laryngeal clefts can occur in families and are likely to be associated with tracheal agenesis, tracheoesophageal fistula, and multiple congenital anomalies, as with G syndrome, Opitz-Frias syndrome, and Pallister-Hall syndrome.

Initial symptoms are those of aspiration and recurrent respiratory infections. Esophagogram is undertaken with extreme caution. Confirmation of the diagnosis is made by direct laryngoscopy and bronchoscopy. Treatment is based on the cleft type and the symptoms. Stabilization of the airway is the first priority. Gastroesophageal reflux must be controlled and a careful assessment for other congenital anomalies is undertaken before repair. Several endoscopic and open cervical and transthoracic surgical repairs have been described.

Bibliography is available at Expert Consult.

386.8 Vascular and Cardiac Anomalies  
James W. Schroeder Jr. and Lauren D. Holinger

The aberrant innominate artery is the most common cause of secondary tracheomalacia (see Chapter 432). It may be asymptomatic and discovered incidentally or it may cause severe symptoms. Expiratory wheezing and cough occur and, rarely, reflex apnea or “dying spells.” Surgical intervention is rarely necessary. Infants are treated expectantly because the problem is self-limited.
Bibliography
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The term *vascular ring* is used to describe vascular anomalies that result from abnormal development of the aortic arch complex. The double aortic arch is the most common complete vascular ring, encircling both the trachea and esophagus, compressing both. With few exceptions, these patients are symptomatic by 3 mo of age. Respiratory symptoms predominate, but dysphagia may be present. The diagnosis is established by barium esophagram that shows a posterior indentation of the esophagus by the vascular ring (see Fig. 432-2 in Chapter 432). CT scan with contrast or MRI with angiography provides the surgeon the information needed.

Other vascular anomalies include the pulmonary artery sling, which also requires surgical correction. The most common open (incomplete) vascular ring is the aberrant right subclavian artery. Although common, it is usually asymptomatic and of academic interest only.

Congenital cardiac defects are likely to compress the left main bronchus or lower trachea. Any condition that produces significant pulmonary hypertension increases the size of the pulmonary arteries, which in turn cause compression of the left main bronchus. Surgical correction of the underlying pathology to relieve pulmonary hypertension relieves the airway compression.

*Bibliography is available at Expert Consult.*

**386.9 Tracheal Stenoses, Webs, and Atresia**  
*James W. Schroeder Jr. and Lauren D. Holinger*

Long-segment congenital tracheal stenosis with complete tracheal rings typically occurs within the 1st yr of life, usually after a crisis has been precipitated by an acute respiratory illness. The diagnosis may be suggested by plain radiographs. CT with contrast delineates associated intrathoracic anomalies such as the pulmonary artery sling, which occurs in one third of patients; one fourth have associated cardiac anomalies. Bronchoscopy is the best method to define the degree and extent of the stenosis and the associated abnormal bronchial branching pattern. Treatment of clinically significant stenosis involves tracheal resection of short segment stenosis, slide tracheoplasty for long segment stenosis. Congenital soft-tissue stenoses and thin webs are rare. Dilation may be all that is required.

*Bibliography is available at Expert Consult.*

**386.10 Foregut Cysts**  
*James W. Schroeder Jr. and Lauren D. Holinger*

The bronchogenic cyst, intramural esophageal cyst (esophageal duplication), and enteric cyst can all produce symptoms of respiratory obstruction and dysphagia. The diagnosis is suspected when chest radiographs or CT scan delineate the mass, and, in the case of enteric cyst, the associated vertebral anomaly. The treatment of all foregut cysts is surgical excision.

*Bibliography is available at Expert Consult.*

**386.11 Tracheomalacia and Bronchomalacia**

See Chapter 389.
Bibliography
Bibliography
Bibliography
EPIDEMIOLOGY AND ETIOLOGY

Choking is a leading cause of morbidity and mortality among children, especially those younger than age 4 yr, largely because of the developmental vulnerabilities of a young child's airway and the underdeveloped ability to swallow food. Infants and toddlers use their mouths to explore their surroundings. Most victims of foreign-body aspiration are older infants and toddlers (Fig. 387-1). Children, younger than 3 yr of age, account for 73% of cases. Preambulatory toddlers can aspirate objects given to them by older siblings. The most common objects that children choke on are food, coins, balloons, and toys. One-third of aspirated objects are nuts, particularly peanuts. Fragments of raw carrot, apple, dried beans, popcorn, and sunflower or watermelon seeds are also aspirated, as are small toys or toy parts. Hard candy and chewing gum are also commonly involved objects. Adolescents may aspirate objects put in their mouth such as pins, jewelry, or blowgun darts. From 1972-1992, 449 deaths from aspirated nonfood foreign bodies among children were reported by the United States Consumer Product Safety Commission. An infant is developmentally able to suck and swallow and also is equipped with involuntary reflexes (gag, cough, and glottis closure) that help to protect against aspiration during swallowing. Dentition develops at approximately 6 mo with eruption of the incisors. Molars do not erupt until approximately 1.5 yr of age; however, mature mastication takes longer to develop. Despite a strong gag reflex, a young child's airway is more vulnerable to obstruction than an adult's airway in several ways. The smaller diameter is more likely to experience significant blockage by small foreign bodies. Mucous and secretions may form a seal around the foreign body, making it more difficult to dislodge by forced air. In addition, the force of air generated by a cough in an infant or young child is less effective in dislodging an airway obstruction. The American Academy of Pediatrics recommends that children younger than 5 yr old should avoid hard candy, chewing gum and that raw fruits and vegetables be cut into small pieces.

The most serious complication of foreign-body aspiration is complete obstruction of the airway. Globular or round food objects such
as hot dogs, grapes, nuts, and candies are the most frequent offenders. Hot dogs are rarely seen as airway foreign bodies because toddlers who choke on hot dogs asphyxiate at the scene unless treated immediately. Complete airway obstruction is recognized in the conscious child as sudden respiratory distress followed by inability to speak or cough.

**CLINICAL MANIFESTATIONS**

Three stages of symptoms may result from aspiration of an object into the airway:

1. **Initial event:** Violent paroxysms of coughing, choking, gagging, and possibly airway obstruction occur immediately when the foreign body is aspirated.
2. **Asymptomatic interval:** The foreign body becomes lodged, reflexes fatigue, and the immediate irritating symptoms subside. This stage is most treacherous and accounts for a large percentage of delayed diagnoses and overlooked foreign bodies. It is during this 2nd stage, when the child is first seen, that the possibility of a foreign-body aspiration is minimized, the physician being reassured by the absence of symptoms that no foreign body is present.
3. **Complications:** Obstruction, erosion, or infection develops to direct attention again to the presence of a foreign body. In this 3rd stage, complications include fever, cough, hemoptysis, pneumonia, and atelectasis.

**DIAGNOSIS**

A positive history must never be ignored. A negative history may be misleading. Choking or coughing episodes accompanied by new onset wheezing are highly suggestive of an airway foreign body. Because nuts are the most common bronchial foreign body, the physician specifically questions the toddler’s parents about nuts. If there is any history of eating nuts, bronchoscopy is carried out promptly.

Most airway foreign bodies lodge in a bronchus (right bronchus ~58% of cases); the location is the larynx or trachea in approximately 10% of cases. Occasionally, fragments of a foreign body may produce bilateral involvement or shifting infiltrates if it moves from lobe to lobe. An esophageal foreign body can compress the trachea and be mistaken for an airway foreign body. The patient is asymptomatic and the radiograph is normal in 15-30% of cases. Opaque foreign bodies occur in only 10-25% of cases. CT can help define radiolucent foreign bodies such as fish bones. If there is a high index of suspicion, bronchoscopy should be performed despite negative imaging studies. History is the most important factor in determining the need for bronchoscopy.

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**TREATMENT**

The treatment of choice for airway foreign bodies is prompt endoscopic removal with rigid instruments. Bronchoscopy is deferred only until preoperative studies have been obtained and the patient has been prepared by adequate hydration and emptying of the stomach. Airway foreign bodies are usually removed the same day the diagnosis is first considered.

### 387.1 Laryngeal Foreign Bodies
**James W. Schroeder Jr. and Lauren D. Holinger**

Complete obstruction asphyxiates the child unless it is promptly relieved with the Heimlich maneuver (see Chapter 67 and Figs. 67-6 and 67-7). Objects that are partially obstructive are usually flat and thin. They lodge between the vocal cords in the sagittal plane, causing symptoms of croup, hoarseness, cough, stridor, and dyspnea.

### 387.2 Tracheal Foreign Bodies
**James W. Schroeder Jr. and Lauren D. Holinger**

Choking and aspiration occurs in 90% of patients with tracheal foreign bodies, stridor in 60%, and wheezing in 50%. Posteroanterior and lateral soft tissue neck radiographs (airway films) are abnormal in 92% of children, whereas chest radiographs are abnormal in only 58%.

### 387.3 Bronchial Foreign Bodies
**James W. Schroeder Jr. and Lauren D. Holinger**

Posteroanterior and lateral chest radiographs are standard in the assessment of infants and children suspected of having aspirated a foreign object. The abdomen is included. A good expiratory posteroanterior chest film is most helpful. During expiration the bronchial foreign body obstructs the exit of air from the obstructed lung, producing obstructive emphysema, air trapping, with persistent inflation of the obstructed lung and shift of the mediastinum toward the opposite side (Fig. 387-2). Air trapping is an immediate complication, in contrast to atelectasis, which is a late finding. Lateral decubitus chest films

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**Figure 387-2 A,** Normal inspiratory chest radiograph in a toddler with a peanut fragment in the left main bronchus. **B,** Expiratory radiograph of the same child showing the classic obstructive emphysema (air trapping) on the involved (left) side. Air leaves the normal right side allowing the lung to deflate. The medium shifts toward the unobstructed side.
or fluoroscopy can provide the same information but are unnecessary. History and physical examination, not radiographs, determine the indication for bronchoscopy.

Bibliography is available at Expert Consult.
Bibliography


Laryngotracheal stenosis is the second most common cause of stridor in neonates and is the most common cause of airway obstruction requiring tracheostomy in infants. The glottis (vocal cords) and the upper trachea are also compromised in most laryngeal stenoses, particularly those that develop following endotracheal intubation. Subglottic stenosis is a narrowing of the subglottic larynx, which is the space extending from the undersurface of the true vocal cords to the inferior margin of the cricoid cartilage. Subglottic stenosis is considered to be congenital when there is no other apparent cause such as a history of laryngeal trauma; approximately 90% of cases manifest in the 1st yr of life.

### 388.1 Congenital Subglottic Stenosis

See Chapter 386.2.

### 388.2 Acquired Laryngotracheal Stenosis

Ninety percent of acquired stenoses are associated with endotracheal intubation, although with improved ventilatory support, the incidence of this complication is decreasing. Studies published after 1983 reported an incidence of neonatal subglottic stenosis of <4%, and those after 1990 reported an incidence of <0.63%. When the pressure of the endotracheal tube against the mucosa is greater than the capillary pressure, ischemia occurs, followed by necrosis and ulceration. Secondary infection and perichondritis develop with exposure of cartilage. Granulation tissue forms around the ulcerations (Fig. 388-1). These changes and edema throughout the larynx usually resolve spontaneously after extubation. Chronic edema and fibrous stenosis develop in only a small percentage of cases. A number of factors predispose to the development of laryngeal stenosis. Laryngopharyngeal reflux of acid and pepsin from the stomach exacerbates endotracheal tube trauma. More damage is caused in areas left unprotected, owing to loss of mucosa. Congenital subglottic stenosis narrows the larynx which makes the patient more likely to develop acquired subglottic stenosis because significant injury is more likely to occur with use of an endotracheal tube of age-appropriate size. Other risk factors for the development of acquired subglottic stenosis include sepsis and infection, dehydration, malnutrition, chronic inflammatory disorders, and immunosuppression. An oversized endotracheal tube is the most common factor contributing to laryngeal injury. A tube that allows a small air leak at the end of the inspiratory cycle minimizes potential trauma. Other extrinsic factors—traumatic intubation, multiple reintubations, movement of the endotracheal tube, and duration of intubation—can contribute to varying degrees in individual patients.

#### CLINICAL MANIFESTATIONS

Symptoms of acquired and congenital stenosis are similar. Spasmodic croup, the sudden onset of severe croup in the early morning hours, is usually caused by laryngopharyngeal reflux with transient laryngospasm and subsequent laryngeal edema. These frightening episodes resolve rapidly, often before the family and child reach the emergency department.

#### DIAGNOSIS

The diagnosis can be made by posteroanterior and lateral airway radiographs and is confirmed by direct laryngoscopy and bronchoscopy. High-resolution CT imaging is of limited value. This is similar to the work-up associated with congenital subglottic stenosis.

#### TREATMENT

The severity, location, and type (cartilaginous or soft tissue) of the stenosis determine the treatment. Mild cases can be managed without operative intervention because the airway will improve as the child grows. Moderate soft-tissue stenosis is treated by endoscopy using gentle dilations or CO₂ laser. Severe laryngotracheal stenosis is likely to require laryngotracheal expansion surgery or resection of the narrowed portion of the laryngeal and tracheal airway (partial cricotracheal resection). Every effort is made to avoid tracheotomy using endoscopic techniques or open surgical procedures.

Bibliography is available at Expert Consult.
Bibliography
Tracheomalacia and bronchomalacia refer to chondromalacia of a central airway, leading to insufficient cartilage to maintain airway patency throughout the respiratory cycle. These are common causes of persistent wheezing in infancy. Tracheomalacia and bronchomalacia can be either primary or secondary (Table 389-1). Primary tracheomalacia and bronchomalacia are often seen in premature infants, although most affected patients are born at term. Secondary tracheomalacia and bronchomalacia refers to the situation in which the central airway is compressed by adjacent structure (e.g., vascular ring; see Chapter 432) or deficient in cartilage because of tracheoesophageal fistula (see Chapter 319). Laryngomalacia can accompany primary bronchomalacia or tracheomalacia. Involvement of the entire central airway (laryngotracheobronchomalacia) is also seen.

CLINICAL MANIFESTATIONS

Primary tracheomalacia and bronchomalacia are principally disorders of infants, with a male:female ratio of 2:1. The dominant finding, low-pitched monophonic wheezing heard predominantly during expiration, is most prominent over the central airways. Parents often describe persistent respiratory congestion even in the absence of a viral respiratory infection. When the lesion involves only 1 main bronchus (more commonly the left), the wheezing is louder on that side, and there may be unilateral palpable fremitus. In cases of tracheomalacia, the wheeze is loudest over the trachea. Hyperinflation and/or subcostal retractions do not occur unless the patient also has concurrent asthma, viral bronchiolitis, or other causes of peripheral airways obstruction. In the absence of asthma, patients with tracheomalacia and bronchomalacia are not helped by administration of a bronchodilator. Acquired tracheomalacia and bronchomalacia are seen in association with vascular compression (vascular rings, slings, and innominate artery compression). Tracheomalacia is the rule following correction of tracheoesophageal fistula. Other causes of acquired tracheomalacia, which may persist after surgical correction, are cardiomegaly. Bronchomalacia is common following lung transplantation, assumed to be secondary to the loss of bronchial artery supply leading to hypoxia of the cartilage. The importance of the physical exam cannot be understated; 1 study found that pediatric pulmonologists made a correct assessment of malacia based on symptoms, history, and lung function prior to bronchoscopy in 74% of cases.

DIAGNOSIS

Definitive diagnoses of tracheomalacia and bronchomalacia are established by flexible or rigid bronchoscopy (Fig. 389-1). The lesion is difficult to detect on plain radiographs. While fluoroscopy can demonstrate dynamic collapse and avoid the need for invasive diagnostic techniques, it is poorly sensitive. Pulmonary function testing can show a pattern of decreased peak flow and flattening of the flow-volume loop. Other important diagnostic modalities include MRI and CT scanning. MRI with angiography is especially useful when there is a possibility of vascular ring and should be performed when a right aortic arch is seen on plain film radiography.

TREATMENT

Postural drainage can help with clearance of secretions. β-Adrenergic agents should be avoided in the absence of asthma, because they can exacerbate loss of airway patency due to decreased airway tone. Nebulized ipratropium bromide may be useful. Endobronchial stents have been used in severely affected patients but have a high incidence of complications, ranging from airway obstruction due to granulation tissue to erosion into adjacent vascular structures. Continuous positive airway pressure via tracheostomy may be indicated for severe cases. Surgical approach (aortopexy and bronchopexy) is rarely required and only for patients who have life-threatening apnea, cyanosis, and bradycardia (“cyanotic spells”) from airway obstruction, and/or who demonstrated vascular compression.

PROGNOSIS

Primary bronchomalacia and tracheomalacia have excellent prognoses, because airflow improves as the child and the airways grow. Patients with primary airway malacia usually take longer to recover from common respiratory infections. Wheezing at rest usually resolves

Table 389-1 Classification of Tracheomalacia

<table>
<thead>
<tr>
<th>PRIMARY TRACHEOMALACIA</th>
<th>SECONDARY TRACHEOMALACIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital absence of tracheal-supporting cartilages</td>
<td>Esophageal atresia, tracheoesophageal fistula</td>
</tr>
<tr>
<td></td>
<td>Vascular rings (double aortic arch)</td>
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<tr>
<td></td>
<td>Tracheal compression from an aberrant innominate artery</td>
</tr>
<tr>
<td></td>
<td>Tracheal compression from mediastinal masses</td>
</tr>
<tr>
<td></td>
<td>Abnormally soft tracheal cartilages associated with connective tissue disorders</td>
</tr>
<tr>
<td></td>
<td>Prolonged mechanical ventilation, chronic lung disease</td>
</tr>
</tbody>
</table>


by age 3 yr. Prolonged bacterial bronchitis has been reported as a complication of bronchomalacia. Prognosis in secondary and acquired forms varies with cause. Patients with concurrent asthma need considerable supportive treatment and careful monitoring of respiratory status.

*Bibliography is available at Expert Consult.*
Bibliography


Vocal nodules, which are not true neoplasms, are the most common cause of chronic hoarseness in children. Chronic vocal abuse or misuse produces nodules at the junction of the anterior and middle thirds of the phonating edge of the vocal cords. These symmetric, bilateral swellings interfere with voice production and cause children to strain the voice. Vocal nodules can occur in infants.

When vocal abuse is the main factor, the voice is worse in the evenings. Voice therapy may be effective in the cooperative child, but for most toddlers and young children, behavioral therapy is necessary. Nodules usually resolve by early teenage years as the child matures and vocal abuse is moderated. Surgical excision is rarely indicated but may be necessary if the child is unable to communicate adequately, becomes aperiodic, or requires tension and straining to make any utterance whatsoever.

When laryngopharyngeal reflux is the main factor, hoarseness is worse in the morning; laryngopharyngeal reflux commonly exacerbates vocal abuse, adding to swelling of the vocal cords. An antireflux regimen is indicated (see Chapter 323.1).

Papillomas are the most common respiratory tract neoplasms in children, occurring in 4.3 in 100,000. They are simply warts—benign tumors—caused by the human papillomavirus (HPV) (see Chapter 266); the same pathology is found in condylomata acuminata (vaginal warts). HPV types 6 and 11 are most commonly associated with laryngeal disease. Although it is a benign disease that usually involves the larynx, recurrent respiratory papillomatosis (RRP) has a predictable clinical course, tends to recur and spread throughout the aerodigestive tract and can undergo malignant conversion. Fifty percent of recurrent RRP cases occur in children younger than age 5 yr, but the diagnosis may be made at any age; 67% of children with RRP are born to mothers who had condylomata during pregnancy or parturition. The mode of HPV transmission is still not clear. The risk for transmission is approximately 1 in 500 vaginal births in mothers with active condylomata. Neonates have been reported to have RRP, suggesting intrauterine transmission of HPV.

**CLINICAL MANIFESTATIONS**

These benign squamous lesions can produce chronic hoarseness in the infant. Most occur in the larynx, specifically on the vocal cords, but in 31% these lesions occur in other areas of the respiratory tract: nose, pharynx (especially the uvula and posterior soft palate), trachea, bronchi, and lungs. As growth of the lesions on the vocal cords progresses, hoarseness increases and communication becomes difficult. Respiratory distress develops. Surgical excision is a quality of life issue that warrants removal to improve the voice. Intervention becomes a medical necessity when airway obstruction progresses (Fig. 390-1). Symptoms often occur first during sleep with symptoms typical of obstructive sleep apnea. Progressive respiratory distress during sleep, exertion, daily activities, and finally at rest indicates the need for surgical intervention.

**TREATMENT**

The treatment of RRP is endoscopic surgical removal. Most surgeons in North America prefer the microdebrider. Laryngopharyngeal reflux can require treatment when reflux laryngitis is a factor. Although surgical management remains the mainstay therapy, some form of adjunct therapy may be needed in up to 20% of cases. The most widely accepted indications for adjunct therapy are a need for more than 4 surgical procedures per year, rapid regrowth of papillomata with airway compromise, or distal multisite spread of disease. Adjunct therapies include antiviral modalities (interferon, ribavirin, acyclovir, cidofovir), photodynamic therapy, dietary supplement (indole-3-carbinol), nonsteroidal antiinflammatory drug (Celebrex), retinoids, and mumps vaccination.

*Bibliography is available at Expert Consult.*

**390.3 Congenital Subglottic Hemangioma**

**CLINICAL MANIFESTATIONS**

Typically, congenital subglottic hemangiomas are symptomatic within the 1st 2 mo of life, almost all occurring before 6 mo of age. Stridor is biphasic but usually more prominent during inspiration. The infant may be hoarse, have a barking cough, and present with croup. Fifty percent of congenital subglottic hemangiomas are associated with facial lesions. Radiographs classically delineate an asymmetric subglottic narrowing. The diagnosis is made by direct laryngoscopy.

**TREATMENT**

The treatment of hemangiomas often requires input from a multispecialty vascular anomalies team. Medical management includes systemic steroids. Prednisone 2–4 mg/kg/day is given orally for 4–6 wk, less if the lesions stabilize sooner. The dosage is then tapered. If there is no response, the drug is discontinued. Propranolol 2-3 mg/kg/day is...
Bibliography


Emerging as a first-line treatment for hemangiomas with the potential to impair function (airway) or cause disfigurement if there are no cardiac or neurovascular contraindications. Although the exact mechanism of action of propranolol is unknown, it has been shown to stop progression and induce involution of hemangiomas in multiple studies. Because side effects include hypotension, bradycardia, bronchospasm, and hypoglycemia, children treated with propranolol need to be monitored closely.

Although tracheostomy establishes a safe airway, every effort should be made to find an alternative. Corticosteroids can also be injected directly into the lesion. Endoscopic excision with the CO₂ laser is effective. Combining several modalities increases the possibility of avoiding tracheostomy. External surgical excision is suitable for some lesions.

Bibliography is available at Expert Consult.

390.4 Vascular Anomalies
James W. Schroeder Jr. and Lauren D. Holinger

Vascular malformations are not true neoplastic lesions. They have a normal rate of endothelial turnover and various channel abnormalities. They are categorized by their predominant type (capillary, venous, arterial, lymphatic, or a combination thereof). Slow-flow malformations have capillary, lymphatic, or venous components. In the past, these were incorrectly called capillary hemangiomas, cystic hygromas, or lymphangiomas, and cavernous hemangiomas, respectively.

Lymphatic malformations (cystic hygromas) rarely occur in the larynx. When they do, they are invariably an extension of disease from elsewhere in the head and neck. Airway obstruction can necessitate tracheostomy. The lesion can be debulked with the CO₂ laser.

Bibliography is available at Expert Consult.

390.5 Other Laryngeal Neoplasms
James W. Schroeder Jr. and Lauren D. Holinger

Neurofibromatosis (see Chapter 596.1) rarely involves the larynx. When children are affected, limited local resection is undertaken to maintain an airway and optimize the voice. Complete surgical extirpation is virtually impossible without debilitating resection of vital laryngeal structures. Most surgeons select the option of less-aggressive symptomatic surgery because of the poorly circumscribed and infiltrative nature of these fibromas. Rhabdomyosarcoma (see Chapter 500) and other malignant tumors of the larynx are rare. Symptoms of hoarseness and progressive airway obstruction prompt initial evaluation by flexible laryngoscopy in the office.

Figure 390-2 A CT scan of the trachea with a circumscribed intraluminal tracheal mass (arrow) in the tracheal wall. (From Venizelos I, Papathomas T, Anagnostou E, et al: Pediatric inflammatory myofibroblastic tumor of the trachea: a case report and review of the literature, Pediatr Pulmonol 43:831–835, 2008.)

390.6 Tracheal Neoplasms
James W. Schroeder Jr. and Lauren D. Holinger

Tracheal tumors include malignant and benign neoplasms. The 2 most common benign tumors are inflammatory pseudotumor and hamartoma. The inflammatory pseudotumor is probably a reaction to a previous bronchial infection or traumatic insult. Growth is slow and the tumor may be locally invasive. Hamartomas are tumors of primary tissue elements that are abnormal in proportion and arrangement.

Tracheal neoplasms manifest with stridor, wheezing, cough, or pneumonia and are rarely diagnosed until 75% of the lumen has been obstructed (Fig. 390-2). Symptoms mimic asthma and are often misdiagnosed as such. Chest radiographs or airway films can identify the obstruction. Pulmonary function studies demonstrate an abnormal flow-volume loop. A mild response to bronchodilator therapy may be misleading. Rational treatment is based upon the histopathology.
Bibliography


Bibliography
DEFINITIONS AND GENERAL PATHOPHYSIOLOGY

Wheezing, the production of a musical and continuous sound that originates from oscillations in narrowed airways, is heard mostly on expiration as a result of critical airway obstruction. Monophonic wheezing refers to a single-pitch sound that is produced in the larger airways during expiration, as in distal tracheomalacia or bronchomalacia. Wheezing is polyphonic when there is widespread narrowing of the airways, causing various pitches as air moves through different levels of obstruction to flow, as seen in asthma. When obstruction occurs in the extrathoracic airways during inspiration, the noise is referred to as stridor.

Infants are more likely to wheeze than older children and adults as a result of a differing set of lung mechanics. The obstruction to flow is affected by the airway caliber and compliance of the infant lung. Resistance to airflow through a tube is inversely related to the radius of the tube to the 4th power. In children younger than 5 yr old, small-caliber
peripheral airways can contribute up to 50% of the total airway resistance. Marginal additional narrowing can cause further flow limitation and a subsequent wheeze.

With the very compliant newborn chest wall, the inward pressure produced in expiration subjects the intrathoracic airways to collapse. Differences in tracheal cartilage composition and airway smooth muscle tone increase the collapsibility of the infant airways in comparison to older children. These mechanisms combine to make the infant more susceptible to airway obstruction, increased resistance, and subsequent wheezing. Many of these conditions are outgrown in the 1st yr of life.

Immunologic and molecular influences can contribute to the infant's propensity to wheeze. In comparison to older children and adults, infants tend to have higher levels of lymphocytes and neutrophils, rather than mast cells and eosinophils, in bronchoalveolar lavage fluid. The childhood wheezing phenotype has been linked to many early exposures including fetal nutrition, maternal smoking, prenatal and birth maternal complications, prenatal and neonatal exposure to antibiotics, exposure to high levels of environmental allergens, and high infant adiposity. Infections during infancy have been cited as risk factors for later wheezing, including respiratory syncytial virus (RSV; see Chapter 260), rhinovirus (see Chapter 263), cytomegalovirus (see Chapter 255), human metapneumovirus (see Chapter 261), bocavirus, adenovirus, and Chlamydia pneumoniae.

A variety of inflammatory mediators have also been implicated in the wheezing infant such as histamine, cytokines, leukotrienes, and interleukins. Taken together, these fetal and/or early postnatal exposures may cause a “programming” of the lung that ultimately affects structure and function.

ETIOLOGY

Although wheezing in infants most frequently results from inflammation (generally bronchiolitis), there are many causes of wheezing (Table 391-1).

Acute Bronchiolitis and Inflammation of the Airway

Infection can cause obstruction to flow by internal narrowing of the airways. Acute bronchiolitis is predominantly a viral disease. RSV is responsible for more than 50% of cases. Other agents include parainfluenza, adenovirus, rhinovirus, and Mycoplasma. Emerging pathogens include human metapneumovirus and human bocavirus, which may be a primary cause of viral respiratory infection or occur as a coinfection with RSV. Although bacterial pneumonia is sometimes confused clinically with bronchiolitis, there is no evidence of a bacterial cause for bronchiolitis and bronchiolitis is rarely followed by bacterial superinfection. Concurrent infection with viral bronchiolitis and pertussis has been described.

Approximately 100,000-126,000 children younger than 1 yr old are hospitalized annually in the United States because of RSV infection. The increasing rates of bronchiolitis that were seen from 1980-1996 (thought to reflect increased attendance of infants in daycare centers, changes in criteria for hospital admission, and/or improved survival of premature infants and others at risk for severe RSV-associated disease), have not continued. In fact, rates have stayed stable in subsequent years despite introduction of routine use of RSV immunoprophylaxis in high-risk populations.

Bronchiolitis is more common in boys, in those who have not been breastfed, and in those who live in crowded conditions. Risk is higher for infants with young mothers or mothers who smoked during pregnancy. Older family members are a common source of infection; they might only experience minor upper respiratory symptoms (colds). The clinical manifestations of lower respiratory tract illness seen in young infants may be minimal in older patients, in whom bronchiolar edema is better tolerated.

Not all infected infants develop lower respiratory tract illness. Host anatomic and immunologic factors play a significant role in the severity of the clinical syndrome, as does the nature of the viral pathogen.
Infants with preexistent smaller airways and diminished lung function have a more severe course. In addition, RSV infection incites a complex immune response. Eosinophils degranulate and release eosinophil cationic protein, which is cytotoxic to airway epithelium. Innate immunity plays a significant role and can depend on polymorphisms in toll-like receptors, interferons, interleukins, and nuclear factor κB. Chemokines and cytokines, such as tumor necrosis factor α, may be differentially expressed, depending on the inciting virus. Coinfection with more than 1 virus can also alter the clinical manifestations and/or severity of presentation.

Acute bronchiolitis is characterized by bronchiolar obstruction with edema, mucus, and cellular debris. Even minor bronchiolar wall thickening significantly affects airflow because resistance is inversely proportional to the 4th power of the radius of the bronchiolar passage. Resistance in the small air passages is increased during both inspiration and exhalation, but because the radius of an airway is smaller during expiration, the resultant respiratory obstruction leads to early air trapping and overinflation. If obstruction becomes complete, trapped distal air will be resorbed and the child will develop atelectasis.

Hypoxemia is a consequence of ventilation–perfusion mismatch early in the course. With severe obstructive disease and tiring of respiratory effort, hypercapnia can develop.

Chronic infectious causes of wheezing should be considered in infants who seem to fall out of the range of a normal clinical course. Cystic fibrosis is one such entity; suspicion increases in a patient with persistent respiratory symptoms, digital clubbing, malabsorption, failure to thrive, electrolyte abnormalities, or a resistance to bronchodilator treatment (see Chapter 403).

Allergy and asthma are important causes of wheezing and probably generate the most questions by the parents of a wheezing infant. Asthma is characterized by airway inflammation, bronchial hyperreactivity, and reversibility of obstruction (see Chapter 144). Three identified patterns of infant wheezing are the transient early wheezer, the persistent wheezer, and the late-onset wheezer. These patterns are seen in 19.9%, 13.7%, and 15% of the general population, respectively, with the remaining 50% of the population never wheezing prior to age 6 yr. Transient early wheezers wheeze at least once with a lower respiratory infection before the age of 3 yr, but never wheeze again. The persistent wheezer has wheezing episodes before age 3 yr and is still wheezing at 6 yr of age. The late-onset wheezer does not wheeze before age 3 yr but is wheezing by 6 yr. Of all the infants who wheezed before 3 yr old, almost 60% stopped wheezing by age 6 yr.

Multiple studies have tried to predict which early wheezers will go on to have asthma in later life. Risk factors for persistent wheezing include parental history of asthma and allergies, maternal smoking, persistent rhinitis (apart from acute upper respiratory tract infections), allergen sensitization, eczema at younger than 1 yr of age, peripheral eosinophilia (≥4%), and frequent episodes of wheezing during infancy.

Other Causes

Congenital malformations of the respiratory tract cause wheezing in early infancy. These findings can be diffuse or focal and can be from an external compression or an intrinsic abnormality. External vascular compression includes a vascular ring, in which the trachea and esophagus are surrounded completely by vascular structures, or a vascular sling, in which the trachea and esophagus are not completely encircled (see Chapter 432). Cardiovascular causes of wheezing include dilated chambers of the heart including massive cardiomegaly, left atrial enlargement, and dilated pulmonary arteries. Pulmonary edema caused by heart failure can also cause wheezing by lymphatic and bronchial vessel engorgement that leads to obstruction and edema of the bronchioles and further obstruction (see Chapter 442).

Foreign-body aspiration (see Chapter 397) can cause acute or chronic wheezing. It is estimated that 78% of those who die from foreign-body aspiration are between 2 mo and 4 yr old. Even in young infants, a foreign body can be ingested if given to the infant by another person, such as an older sibling. Infants who have atypical histories or misleading clinical and radiologic findings can receive a misdiagnosis of asthma or another obstructive disorder as inflammation and granulation develop around the foreign body. An esophageal foreign body can transmit pressure to the membranous trachea, causing compromise of the airway lumen.

Gastroesophageal reflux (see Chapter 323.1) can cause wheezing with or without direct aspiration into the tracheobronchial tree. Without aspiration, the reflux is thought to trigger a vagal or neural reflex, causing increased airway resistance and airway reactivity. Aspiration from gastroesophageal reflux or from the direct aspiration from oral liquids can also cause wheezing.

Trauma and tumors are much rarer causes of wheezing in infants. Trauma of any type to the tracheobronchial tree can cause an obstruction to airflow. Accidental or nonaccidental aspirations, burns, or scalds of the tracheobronchial tree can cause inflammation of the airways and subsequent wheezing. Any space-occupying lesion, either in the lung itself or extrinsic to the lung, can cause tracheobronchial compression and obstruction to airflow.

CLINICAL MANIFESTATIONS

History and Physical Examination

The initial history of a wheezing infant should describe the recent event including onset, duration, and associated factors (Table 391-2). Birth history includes weeks of gestation, neonatal intensive care unit admission, history of intubation or oxygen requirement, maternal complications including infection with herpes simplex virus or HIV, and prenatal smoke exposure. Past medical history includes any comorbid conditions including syndromes or associations. Family history of cystic fibrosis, immunodeficiencies, asthma in a 1st-degree relative, or any other recurrent respiratory conditions in children should be obtained. Social history should include an environmental history including any smokers at home, inside or out, daycare exposure, number of siblings, occupation of inhabitants of the home, pets, tuberculosis exposure, and concerns regarding home environment (e.g., dust mites, construction dust, heating and cooling techniques, mold, cockroaches). The patient’s growth chart should be reviewed for signs of failure to thrive.

On physical examination, evaluation of the patient’s vital signs with special attention to the respiratory rate and the pulse oximetry reading for oxygen saturation is an important initial step. The exam is often dominated by wheezing. Auscultation might reveal fine crackles or overt wheezes, with prolongation of the expiratory phase of breathing.

<table>
<thead>
<tr>
<th>Table 391-2</th>
<th>Pertinent Medical History in the Wheezing Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the onset of symptoms begin at birth or thereafter?</td>
<td></td>
</tr>
<tr>
<td>Is the infant a noisy breather and when is it most prominent?</td>
<td></td>
</tr>
<tr>
<td>Is the noisy breathing present on inspiration, expiration, or both?</td>
<td></td>
</tr>
<tr>
<td>Is there a history of cough apart from wheezing?</td>
<td></td>
</tr>
<tr>
<td>Was there an earlier lower respiratory tract infection?</td>
<td></td>
</tr>
<tr>
<td>Is there a history of recurrent upper or lower respiratory tract infections?</td>
<td></td>
</tr>
<tr>
<td>Have there been any emergency department visits, hospitalizations, or intensive care unit admissions for respiratory distress?</td>
<td></td>
</tr>
<tr>
<td>Is there a history of eczema?</td>
<td></td>
</tr>
<tr>
<td>Does the infant cough after crying or cough at night?</td>
<td></td>
</tr>
<tr>
<td>How is the infant growing and developing?</td>
<td></td>
</tr>
<tr>
<td>Is there associated failure to thrive?</td>
<td></td>
</tr>
<tr>
<td>Is there a history of electrolyte abnormalities?</td>
<td></td>
</tr>
<tr>
<td>Are there signs of intestinal malabsorption including frequent, greasy, or oily stools?</td>
<td></td>
</tr>
<tr>
<td>Is there a maternal history of genital herpes simplex virus infection?</td>
<td></td>
</tr>
<tr>
<td>What was the gestational age at delivery?</td>
<td></td>
</tr>
<tr>
<td>Was the patient intubated as a neonate?</td>
<td></td>
</tr>
<tr>
<td>Does the infant bottle-feed in the bed or the crib, especially in a propped position?</td>
<td></td>
</tr>
<tr>
<td>Are there any feeding difficulties including choking, gagging, arching, or vomiting with feeds?</td>
<td></td>
</tr>
<tr>
<td>Is there any new food exposure?</td>
<td></td>
</tr>
<tr>
<td>Is there a toddler in the home or lapse in supervision in which foreign-body aspiration could have occurred?</td>
<td></td>
</tr>
<tr>
<td>Change in caregivers or chance of nonaccidental trauma?</td>
<td></td>
</tr>
</tbody>
</table>
Wheezein produces an expiratory whistling sound that can be polyphonic or monophonic. Expiratory time may be prolonged. Biphasic wheezing can occur if there is a central, large airway obstruction. The degree of tachypnea does not always correlate with the degree of hypoxemia or hypercarbia, so pulse oximetry and noninvasive determination of carbon dioxide is essential. Work of breathing may be markedly increased, with nasal flaring and retractions. Complete obstruction to airflow can eliminate the turbulence that causes wheezing; thus the lack of audible wheezing is not reassuring if the infant shows other signs of respiratory distress. Barely audible breath sounds suggest very severe disease with nearly complete broncholar obstruction.

Aeration should be noted and a trial of a bronchodilator may be warranted to evaluate for any change in wheezing after treatment. Listening to breath sounds over the neck helps differentiate upper airway from lower airway sounds. The absence or presence of stridor should be noted and appreciated on inspiration. Signs of respiratory distress include tachypnea, increased respiratory effort, nasal flaring, tracheal tugging, subcostal and intercostal retractions, and excessive use of accessory muscles. In the upper airway, signs of atopy, including boggy turbinates and posterior oropharynx cobblestoning, can be evaluated in older infants. It is also useful to evaluate the skin of the patient for eczema and any significant hemangiomas; midline lesions may be associated with an intrathoracic lesion. Digital clubbing should be noted (see Chapter 374). Hyperinflation of the lungs can permit palpation of the liver and spleen.

Acute bronchiolitis is usually preceded by exposure to an older contact with a minor respiratory syndrome within the previous week. The infant first develops a mild upper respiratory tract infection with sneezing and clear rhinorrhea. This may be accompanied by diminished appetite and fever of 38.5-39°C (101-102°F), although the temperature can range from subnormal to markedly elevated. Gradually, respiratory distress ensues, with paroxysmal wheezy cough, dyspnea, and irritability. The infant is often tachypneic, which can interfere with feeding. The child does not usually have other systemic complaints, such as diarrhea or vomiting. Apnea may be more prominent than wheezing early in the course of the disease, particularly with very young infants (<2 mo old) or former premature infants.

**Diagnostic Evaluation**

Initial evaluation depends on likely etiology; a baseline chest radiograph, including posteroanterior and lateral films, is warranted in many cases and for any infant in acute respiratory distress, but not routinely indicated in children with uncomplicated bronchiolitis. Infiltrates are most often found in wheezing infants who have a pulse oximetry reading <93%, grunting, decreased breath sounds, prolonged inspiratory to expiratory ratio, and crackles. Pulse oximetry is indicated as hypoxia is common in bronchiolitis and may signify diffuse involvement, air trapping, ventilation-perfusion mismatching, and atelectasis. The chest radiograph may also be useful for evaluating hyperinflation (common in bronchiolitis and viral pneumonia), atelectasis signs of chronic disease such as bronchectasis, or a space-occupying lesion causing airway compression. A trial of bronchodilator may be diagnostic as well as therapeutic because these medications can reverse conditions such as asthma but will not affect a fixed obstruction. Bronchodilators potentially can worsen a case of wheezing caused by tracheal or bronchial malacia. A sweat test to evaluate for cystic fibrosis and evaluation of baseline immune status are reasonable in infants with recurrent wheezing, failure to thrive, or complicated courses. Further evaluation such as upper gastrointestinal contrast x-rays, chest CT, bronchoscopy, bronchoalveolar lavage, ciliary biopsy, infant pulmonary function testing, video swallow study, and pH probe can be considered 2nd-tier diagnostic procedures in complicated patients.

The diagnosis of acute bronchiolitis is clinical, particularly in a previously healthy infant presenting with a 1st-time wheezing episode during a community outbreak. Chest radiography can reveal hyperinflated lungs with patchy atelectasis but is not indicated in all patients with bronchiolitis. The white blood cell and differential counts are usually normal. Viral testing (polymerase chain reaction, rapid immuno

### Treatment

Treatment of an infant with wheezing depends on the underlying etiology. Response to bronchodilators is unpredictable, regardless of cause, but suggests a component of bronchial hyperreactivity. It is appropriate to administer albuterol aerosol and objectively observe the response. For children younger than 3 yr of age, it is acceptable to continue to administer inhaled medications through a metered-dose inhaler with mask and spacer if a therapeutic benefit is demonstrated. Therapy should be continued in all patients with asthma exacerbations from a viral illness.

The use of ipratropium bromide in this population is controversial, but it appears to be somewhat effective as an adjunct therapy. It is also useful in infants with significant tracheal and bronchial malacia who may be made worse by β2-agonists such as albuterol because of the subsequent decrease in smooth muscle tone.

A trial of inhaled steroids may be warranted in a patient who has responded to multiple courses of oral steroids and who has moderate to severe wheezing or a significant history of atopy including food allergy or eczema. Inhaled corticosteroids are appropriate for maintenance therapy in patients with known reactive airways but are controversial when used for episodic or acute illnesses. Intermittent, high-dose inhaled corticosteroids are not recommended for intermittent wheezing. Early use of inhaled corticosteroids has not been shown to prevent the progression of childhood wheezing or affect the natural history of asthma in children.

Oral steroids are generally reserved for atopic wheezing infants thought to have asthma that is refractory to other medications. Their use in 1st-time wheezing infants or in infants who do not warrant hospitalization is controversial.

Infants with acute bronchiolitis who are experiencing respiratory distress (hypoxia, inability to take oral feedings, apnea, extreme tachypnea) should be hospitalized; risk factors for severe disease include age <12 wk, preterm birth, or underlying comorbidity such as cardiovascular, pulmonary, neurologic, or immunologic disease. The mainstay of treatment is supportive. Hypoxemic children should receive cool humidified oxygen. Sedatives are to be avoided because they can depress respiratory drive. The infant is sometimes more comfortable if sitting with head and chest elevated at a 30-degree angle with neck extended. There is a small risk of aspiration of oral feedings in infants with bronchiolitis, owing to tachypnea and the increased work of breathing. If there is any risk for further respiratory decompensation potentially necessitating tracheal intubation, the infant should not be fed orally but be maintained with parenteral fluids. Frequent suctioning of nasal and oral secretions often provides relief of distress or cyanosis. Suctioning of secretions is an essential part of the treatment of bronchiolitis. Oxygen is definitely indicated in all infants with hypoxia. High-flow nasal cannula therapy can reduce the need for intubation in patients with impending respiratory failure.

A number of agents have been proposed as adjunctive therapies for bronchiolitis. Bronchodilators may produce short-term improvement in clinical features. This must be placed in context of potential adverse effects and the lack of any evidence indicating improvement in overall course of the disease. Systematic reviews and meta-analyses of randomized controlled trials have failed to show a benefit from bronchodilators in uncomplicated bronchiolitis. Corticosteroids, whether parenteral, oral, or inhaled, have been used for bronchiolitis despite conflicting and often negative studies. Corticosteroids are not recommended in previously healthy infants with RSV. Ribavirin, an antiviral agent administered by aerosol, has been used for infants with RSV who have congenital heart disease or chronic lung disease. There is no convincing evidence of a positive impact on clinically important
outcomes such as mortality and duration of hospitalization. Antibiotics have no value unless there is coexisting bacterial infection. Likewise, there is no support for RSV immunoglobulin administration during acute episodes of RSV bronchiolitis in previously healthy children. Combined therapy with nebulized epinephrine and dexamethasone has been used with some success, but additional studies are needed to confirm its efficacy and investigate the long-term adverse effects in infants before this combination can be recommended. Nebulized hypertonic saline has been reported to have some benefit, and may shorten hospital length of stay. One study suggested that on demand therapy with inhaled epinephrine or saline was more effective than scheduled fixed dosing. Heliox delivered by tight fitting mask or by continuous positive airway pressure has been of some benefit in moderately to severely affected patients with bronchiolitis.

Certain (10%) low risk patients with bronchiolitis and an oxygen requirement may be discharged from the emergency department to receive home oxygen therapy. Criteria for home oxygen therapy includes: typical clinical features (no apnea, wheezing ≥ 1), 2 mo-2 yr of age (>4 wk gestational age); first episode of wheezing; illness during RSV season; secretions managed by parents with bulb suctioning; smoke free home; reliable family with good access to healthcare; altitude ≤ 6,000 feet; absence of toxic appearance or proven bacterial disease; apparent life-threatening event; cardiac, pulmonary, immunodeficiency, or neuromuscular disorders; baseline oxygen requirement prior to current illness; mild illness as evident by feeding well and alert and active; minimal retractions; respiratory rate <50 breaths/min; oxygenation >90% on ≤ 0.5 L/min of oxygen. All patients must have follow-up within 24 hr of discharge from the emergency room by their primary care provider or by the emergency room staff. Chest physiotherapy does not improve disease course in hospitalized infants with bronchiolitis who are not mechanically ventilated.

PROGNOSIS
Infants with acute bronchiolitis are at highest risk for further respiratory compromise in the 1st 48-72 hr after onset of cough and dyspnea; the child may be desperately ill with air hunger, apnea, and respiratory acidosis. The case fatality rate is <1%, with death attributable to apnea, respiratory arrest, or severe dehydration. After this critical period, symptoms can persist. The median duration of symptoms in ambulatory patients is approximately 14 days; 10% may be asymptomatic at 3 wk. There is a higher incidence of wheezing and asthma in children with a history of bronchiolitis unexplained by family history or other atopic syndromes. It is unclear whether bronchiolitis incites an immune response that manifests as asthma later or whether those infants have an inherent predilection for asthma that is merely unmasked by their episode of viral bronchiolitis.

PREVENTION
Reduction in the severity and incidence of acute bronchiolitis because of RSV is possible through the administration of pooled hyperimmune RSV intravenous immunoglobulin and palivizumab, an intramuscular monoclonal antibody to the RSV F protein, before and during RSV season. Palivizumab should be considered for infants younger than 2 yr of age with chronic lung disease, a history of prematurity, and some forms of congenital heart disease (see Chapter 260). Meticulous hand hygiene is the best measure to prevent nosocomial transmission.

Bibliography is available at Expert Consult.

391.2 Bronchitis
Lauren E. Camarda and Denise M. Goodman

Nonspecific bronchial inflammation is termed bronchitis and occurs in multiple childhood conditions. Acute bronchitis is a syndrome, usually viral in origin, with cough as a prominent feature. Acute tracheobronchitis is a term used when the trachea is prominently involved. Nasopharyngitis may also be present, and a variety of viral and bacterial agents, such as those causing influenza, pertussis, and diphtheria, may be responsible. Isolation of common bacteria such as Staphylococcus aureus and Streptococcus pneumoniae from the sputum might not imply a bacterial cause that requires antibiotic therapy.

ACUTE BRONCHITIS
Clinical Manifestations
Acute bronchitis often follows a viral upper respiratory tract infection. It is more common in the winter when respiratory viral syndromes predominate. The tracheobronchial epithelium is invaded by the infectious agent, leading to activation of inflammatory cells and release of cytokines. Constitutional symptoms including fever and malaise follow. The tracheobronchial epithelium can become significantly damaged or hypersensitized, leading to a protracted cough lasting 1-3 wk.

The child first presents with nonspecific upper respiratory infectious symptoms, such as rhinitis. Three to 4 days later, a frequent, dry, hacking cough develops, which may or may not be productive. After several days, the sputum can become purulent, indicating leukocyte migration but not necessarily bacterial infection. Many children swallow their sputum which can produce emesis. Chest pain may be a prominent complaint in older children and is exacerbated by coughing. The mucus gradually thickens, usually within 5-10 days, and then the cough gradually abates. The entire episode usually lasts about 2 wk and seldom longer than 3 wk.

Findings on physical examination vary with the age of the patient and stage of the disease. Early findings are absent or include low-grade fever and upper respiratory signs such as nasopharyngitis, conjunctivitis, and rhinitis. Auscultation of the chest may be unremarkable at this early phase. As the syndrome progresses and cough worsens, breath sounds become coarse, with coarse and fine crackles and scattered high-pitched wheezing. Chest radiographs are normal or can have increased bronchial markings.

The principal objective of the clinician is to exclude pneumonia, which is more likely caused by bacterial agents requiring antibiotic therapy. Absence of abnormality of vital signs (tachycardia, tachypnea, fever) and a normal physical examination of the chest reduce the likelihood of pneumonia.

Differential Diagnosis
Persistent or recurrent symptoms should lead the clinician to consider entities other than acute bronchitis. Many entities manifest with cough as a prominent symptom (Table 391-3).

Treatment
There is no specific therapy for acute bronchitis. The disease is self-limited, and antibiotics, although often prescribed, do not hasten improvement. Frequent shifts in position can facilitate pulmonary drainage in infants. Older children are sometimes more comfortable with humidity, but this does not shorten the disease course. Cough suppressants can relieve symptoms but can also increase the risk of suppuration and inspissated secretions and, therefore, should be used judiciously. Antihistamines dry secretions and are not helpful; expectorants are likewise not indicated. Nonprescription cough and cold medicines should not be used in children younger than 2 yr of age and their use is cautioned in children age 2-11 yr.

CHRONIC BRONCHITIS
Chronic bronchitis is well recognized in adults, formally defined as 3 mo or longer of productive cough each year for 2 or more yr. The disease can develop insidiously, with episodes of acute obstruction alternating with quiescent periods. A number of predisposing conditions can lead to progression of airflow obstruction or chronic obstructive pulmonary disease, with smoking as the major factor (up to 80% of patients have a smoking history). Other conditions include air pollution, occupational exposures, and repeated infections. In children, cystic fibrosis, bronchopulmonary dysplasia, and bronchiectasis must be ruled out.

The applicability of this definition to children is unclear. The existence of chronic bronchitis as a distinct entity in children is
Bibliography


Committee on Infectious Diseases and Bronchiolitis Guidelines committee: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection, *Pediatrics* 134:e620–e638, 2014.


Plastic bronchitis is a rare condition characterized by recurrent episodes of airway obstruction secondary to the formation of large proteinaceous branching casts that take on the shape of and obstruct the tracheobronchial tree. It is not a single disease entity, but rather represents an altered state of respiratory epithelial function and is most frequently encountered in the setting of underlying pulmonary or congenital cardiac disease, although there have been reports of plastic bronchitis complicating lymphangitic disorders, pulmonary infections, and the acute chest syndrome of sickle cell disease. In comparison to the smaller bronchial and bronchiolar casts seen with mucus plugging, the lesions of plastic bronchitis are more extensive, with casts that can outline large segments of the airway to the level of the terminal bronchioles (Fig. 391-1). These casts may be spontaneously expectorated or may require bronchosscopic removal for relief of potentially fatal airway obstruction. Cast composition varies, though typically consists of either a fibrin-predominant or mucin-predominant laminated matrix with or without inflammatory cell infiltration. Plastic bronchitis may be classified according to an associated disease, the cast histology, or a combination.

### EPIDEMIOLOGY
Plastic bronchitis is rare, and its true prevalence in the pediatric population is not known but is estimated to be 6.8 cases per 100,000 patients. Prevalence does vary in relation to the underlying associated disease state, with rates as high as 14% estimated in patients who have undergone staged palliation of complex cyanotic congenital heart disease, and much lower rates seen complicating asthma and atopic disease. A slight male predominance exists for cast formation in the setting of structural heart disease, whereas cast formation in the setting of asthma and atopic disease demonstrates a female predominance.

### PATHOGENESIS
The mechanism of cast formation is unclear, although it is believed to vary based on the underlying disease association and cast type. One classification system differentiates type 1 inflammatory casts, composed of primarily of fibrin with neutrophilic and more often eosinophilic infiltration, and type 2 casts, composed primarily of mucin with little to no cellular infiltration. Type 1 casts may be associated with inflammatory and infectious disorders of the lung, while type 2 casts may be associated with structural heart disease. However, these distinctions are not absolute; patients with structural heart disease can have mucin-predominant casts and patients with asthma or atopic disease can have fibrin-predominant casts, with both mucin casts and fibrin casts demonstrating various degrees of cellular infiltration. Cast formation in the setting of structural heart disease may result from alterations in pulmonary blood flow or from alterations in lymphatic drainage, either congenital or secondary to the protein-losing enteropathy associated with Fontan physiology. Mucin-predominant casts are believed to arise secondary to mucus gland hypersecretion as well as decreased mucociliary clearance.

### CLINICAL MANIFESTATIONS
Patients with plastic bronchitis may present with cough, dyspnea, wheeze, or pleuritic chest pain. Depending on the degree of airway obstruction, patients may be hypoxemic or in severe respiratory distress. The expectoration of large, branched casts that are often tan in color may provide a clue to the diagnosis. The casts are typically composed of a combination of fibrin and mucin, often with a fibrin-predominant lamina.
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Bibliography
color and rubbery in consistency is pathognomonic for plastic bronchitis. Lung examination may reveal diminished breath sounds or wheezing in the affected area. Rarely, auscultation may reveal a sound similar to a flag flapping in the wind (bruit de drapeau), believed to be related to the free end of a cast striking the bronchial wall during inspiration or expiration. Further examination may provide clues to underlying comorbidities.

**DIAGNOSIS**

The expectoration or endoscopic discovery of large tracheobronchial casts is pathognomonic for plastic bronchitis. History should be directed at assessing for conditions known to be associated with risk of tracheobronchial cast formation, such as uncorrected or surgically palliated complex congenital heart disease; a history of atopic disease or asthma; lymphangitic disorders such as Noonan syndrome, Turner syndrome, lymphangiectasia, and yellow nail syndrome; sickle cell disease; and infectious exposures, particularly exposure to tuberculosis or atypical mycobacteria. Other predisposing conditions include cystic fibrosis, allergic bronchopulmonary aspergillosis, bronchiectasis, toxic inhalants, and granulomatous lung diseases.

Physical examination may provide indications of an underlying diagnosis. Digital clubbing of the fingers or toes may suggest long-standing hypoxemia associated with cardiac or pulmonary disease. Cardiac examination may provide information suggesting the presence of unrecognized structural heart disease.

Chest radiography may demonstrate collapse of the involved areas of the lung, or areas of bronchiectasis distal to sites of long-standing obstruction.

There should be a high index of suspicion for plastic bronchitis in patients with known comorbidities who present with sudden respiratory decompensation. In the absence of cast expectoration, direct visualization of casts via bronchoscopy is required for diagnosis and is potentially therapeutic in relieving airway obstruction. Cast histology should be defined so as to allow for specific therapies directed at preventing recurrence. In particular, the predominant component of the cast’s laminated matrix—either fibrin or mucin—should be defined, and signs of inflammation or infiltration, such as the presence of neutrophils, eosinophils, or Charcot-Leyden crystals, should be documented.

**TREATMENT**

Treatment is directed at correcting the underlying condition associated with the development of plastic bronchitis, at relieving acute airway obstruction secondary to the presence of casts, and at preventing the development of further casts. Rigid or flexible bronchoscopy is typically required for cast removal. If the predominant content of the cast is known, therapy with either mucolytics or fibrinolytics may be considered as an adjunct to direct removal, and aerosolized fibrinolytics such as tissue plasminogen activator or mucolytics such as N-acetylcysteine or deoxyribonuclease may be used for prevention of recurrence. Bronchodilators should be used appropriately in the setting of reactive airway disease, and inhaled or systemic corticosteroids, low-dose azithromycin, and leukotriene inhibitors may be used to minimize airway inflammation. MRI lymphangiography may identify abnormal lymphatic vessels that may benefit from lymphatic embolization procedures.

**COMPLICATIONS AND PROGNOSIS**

Prognosis is related primarily to the underlying condition associated with the development of plastic bronchitis. Patients whose plastic bronchitis is related to surgically palliated complex congenital heart disease are at high risk for plastic bronchitis-related mortality. Mortality can be high if casts obstruct significant portions of the airway, regardless of underlying etiology. Mortality estimates vary from 6-50% in the setting of asthma or atopic disease, and from 28-60% in the setting of complex congenital heart disease, with central airway obstruction leading to death in the majority of patients.

*Bibliography is available at Expert Consult.*
Chapter 391 - Wheezing, Bronchiolitis, and Bronchitis

**Bibliography**


Pulmonary emphysema consists of distention of air spaces with irreversible disruption of the alveolar septa. It can involve part or all of a lung. Overinflation is distention with or without alveolar rupture and is often reversible. Compensatory overinflation can be acute or chronic and occurs in normally functioning pulmonary tissue when, for any reason, a sizable portion of the lung is removed or becomes partially or completely airless, which can occur with pneumonia, atelectasis, empyema, and pneumothorax. Obstructive overinflation results from partial obstruction of a bronchus or bronchiole, when it becomes more difficult for air to leave the alveoli than to enter. Air gradually accumulates distal to the obstruction, the so-called bypass, ball-valve, or check-valve type of obstruction.

**LOCALIZED OBSTRUCTIVE OVERINFLATION**

When a ball-valve type of obstruction partially occludes the main stem bronchus, the entire lung becomes overinflated; individual lobes are affected when the obstruction is in lobar bronchi. Segments or subsegments are affected when their individual bronchi are blocked. When most or all of a lobe is involved, the percussion note is hyperresonant over the area, and the breath sounds are decreased in intensity. The distended lung can extend across the mediastinum into the opposite hemithorax. Under fluoroscopic scrutiny during exhalation, the overinflated area does not decrease, and the heart and the mediastinum shift to the opposite side because the unobstructed lung empties normally.

**Unilateral Hyperlucent Lung**

The differential diagnosis for of this resultant unilateral hyperlucent lung is quite broad and can involve the lung parenchyma, airways, pulmonary vasculature, chest wall (see Chapter 417), and mediastinum. Localized obstructions that can be responsible for overinflation include airway foreign bodies and the inflammatory reaction to them (see Chapter 387), abnormally thick mucus (cystic fibrosis, Chapter 403), endobronchial tuberculosis or tuberculosis of the tracheobronchial lymph nodes (see Chapter 215), and endobronchial or mediastinal tumors. Patients with unilateral hyperlucent lung can present with clinical manifestations of pneumonia, but in some patients the condition is discovered only when a chest radiograph is obtained for an unrelated reason. A few patients have hemoptysis. Physical findings can include hyperresonance and a small lung with the mediastinum shifted toward the more abnormal lung.

**Swyer-James or Macleod Syndrome**

The condition is thought to result from an insult to the lower respiratory tract following most commonly adenovirus (see Chapter 262), or respiratory syncytial virus (see Chapter 260), *Mycoplasma pneumoniae* (see Chapter 223), or measles (see Chapter 246). Clinically, children with this condition often have chronic cough, recurrent pneumonia, and wheezing, although some are asymptomatic. Some patients show a classic mediastinal shift away from the lesion with exhalation. CT scanning or bronchography can often demonstrate bronchiectasis. Ventilation–perfusion scans can be helpful in the diagnosis. In some patients, previous chest radiographs have been normal or have shown only an acute pneumonia, suggesting that a hyperlucent lung is an acquired lesion. No specific treatment is known; it may become less symptomatic with time. Indications as to which children would benefit from surgery remain controversial.
Congenital Lobar Emphysema

Congenital lobar emphysema (CLE) can result in severe respiratory distress in early infancy and can be caused by localized obstruction. Familial occurrence has been reported. In 50% of cases, a cause of CLE can be identified. Congenital deficiency of the bronchial cartilage, external compression by aberrant vessels, bronchial stenosis, redundant bronchial mucosal flaps, and kinking of the bronchus caused by herniation into the mediastinum have been described as leading to bronchial obstruction and subsequent CLE and commonly affects the left upper lobe.

Clinical manifestations usually become apparent in the neonatal period but are delayed for as long as 5-6 mo in 5% of patients. Many cases are diagnosed by antenatal ultrasonography. Babies with prenatally diagnosed cases are not always symptomatic at birth. In some patients, CLE remains undiagnosed until school age or beyond. Clinical signs range from mild tachypnea and wheeze to severe dyspnea with cyanosis. CLE can affect 1 or more lobes; it affects the upper and middle lobes, and the left upper lobe is the most common site. The affected lobe is essentially nonfunctional because of the overdistention, with impaired function seen as well (Fig. 392-1). A radiolucent lobe and a flattened chest during exhalation is observed. The percussion note is hyperresonant. On auscultation, the inspiratory phase is usually less prominent than the expiratory phase, which is prolonged and roughened. Fine or medium crackles may be heard. Cyanosis is more common in the severe cases.

Pathology

In chronic overinflation, many of the alveoli are ruptured and communicate with one another, producing distended saccules. Air can also enter the interstitial tissue (i.e., interstitial emphysema), resulting in pneumomediastinum and pneumothorax (see Chapters 412 and 411).

Clinical Manifestations

Generalized obstructive overinflation is characterized by dyspnea, with difficulty in exhaling. The lungs become increasingly overdistended, and the chest remains expanded during exhalation. An increased respiratory rate and decreased respiratory excursion result from the overdistention of the alveoli and their inability to be emptied normally through the narrowed bronchioles. Air hunger is responsible for forced respiratory movements. Overaction of the accessory muscles of respiration results in retractions at the suprasternal notch, the supraclavicular spaces, the lower margin of the thorax, and the intercostal spaces. Unlike the flattened chest during inspiration and exhalation in cases of laryngeal obstruction, minimal reduction in the size of the overdistended chest during exhalation is observed. The percussion note is hyperresonant. On auscultation, the inspiratory phase is usually less prominent than the expiratory phase, which is prolonged and roughened. Fine or medium crackles may be heard. Cyanosis is more common in the severe cases.

Pulmonary Vascular Abnormalities

Unilateral hyperlucency may result from unilateral pulmonary agenesis (see Chapter 395) that typically presents in the neonatal period. Volume loss of the affected lung results in a mediastinal shift with hyperinflation of the contralateral lung. An anomalous origin of the left pulmonary artery (see Chapter 432), also known as a pulmonary artery sling, can impinge the right mainstem bronchus with resultant right-sided hyperinflation or atelectasis producing hyperlucency on either the ipsilateral or contralateral side. Pulmonary venolobar syndrome (see Chapter 426), also known as scimitar syndrome, can also result in a hyperlucent contralateral lung dependent on the extent of hypoplasia of the right lung.

Generalized Obstructive Overinflation

Acute generalized overinflation of the lung results from widespread involvement of the bronchioles and is usually reversible. It occurs more commonly in infants than in children and may be secondary to a number of clinical conditions, including asthma, cystic fibrosis, acute bronchiolitis, interstitial pneumonitis, atypical forms of acute laryngotracheobronchitis, aspiration of zinc stearate powder, chronic passive congestion secondary to a congenital cardiac lesion, and miliary tuberculosis.

Treatment

by immediate surgery and excision of the lobe may be lifesaving when cyanosis and severe respiratory distress are present, but some patients respond to medical treatment. Selective intubation of the unaffected lung may be of value. Some children with apparent CLE have reversible overinflation, without the classic alveolar septal rupture implied in the term emphysema. Bronchoscopy can reveal an endobronchial lesion.

Surgical excision

• Chest x-ray
• CT
• Severe symptoms
• Moderate herniation of lung
• No perfusion defect
• Bronchoscopy
• Abnormal

Conservative management with close follow up

• Chest x-ray
• CT
• Mild to moderate symptoms
• Moderate herniation of lung
• Bronchoscopy
• Normal
Respiratory System

Part XIX

Sema is usually a self-limited process and requires no specific treatment. Minimization of activities that can increase airway pressure (cough, performance of high-pressure pulmonary function testing maneuvers) is recommended. Resolution occurs by resorption of subcutaneous air after elimination of its source. Rarely, dangerous compression of the trachea by air in the surrounding soft tissue requires surgical intervention.

Bibliography is available at Expert Consult.

**Diagnosis**

Radiographic and fluoroscopic examinations of the chest assist in establishing the diagnosis. Both leaves of the diaphragm are low and flattened, the ribs are farther apart than usual, and the lung fields are less dense. The movement of the diaphragm during exhalation is decreased, and the excursion of the low, flattened diaphragm in severe cases is barely discernible. The anteroposterior diameter of the chest is increased, and the sternum may be bowed outward.

**Bullous Emphysema**

Bullous emphysematous blebs or cysts (pneumatoceles) result from overdistention and rupture of alveoli during birth or shortly thereafter, or they may be sequelae of pneumonia and other infections. They have been observed in tuberculosis lesions during specific antibacterial therapy. These emphysematous areas presumably result from rupture of distended alveoli, forming a single or multiloculated cavity. The cysts can become large and might contain some fluid; an air–fluid level may be demonstrated on the radiograph (Fig. 392-3). The cysts should be differentiated from pulmonary abscesses. In most cases, the cysts disappear spontaneously within a few months, although they can persist for a year or more. Aspiration or surgery is not indicated except in cases of severe respiratory and cardiac compromise.

Subcutaneous emphysema results from any process that allows free air to enter into the subcutaneous tissue (Fig. 392-4). The most common causes include pneumomediastinum or pneumothorax. Additionally, it can be a complication of fracture of the orbit, which permits free air to escape from the nasal sinuses. In the neck and thorax, subcutaneous emphysema can follow tracheotomy, deep ulceration in the pharyngeal region, esophageal wounds, or any perforating lesion of the larynx or trachea. It is occasionally a complication of thoracentesis, asthma, or abdominal surgery. Rarely, air is formed in the subcutaneous tissues by gas-producing bacteria.

Tenderness over the site of emphysema and a crepitant quality on palpation of the skin are classic manifestations. Subcutaneous emphysema is usually a self-limited process and requires no specific treatment. Minimization of activities that can increase airway pressure (cough, performance of high-pressure pulmonary function testing maneuvers) is recommended. Resolution occurs by resorption of subcutaneous air after elimination of its source. Rarely, dangerous compression of the trachea by air in the surrounding soft tissue requires surgical intervention.

Bibliography is available at Expert Consult.
Bibliography
Although it rarely causes lung disease in children, homozygous deficiency of α₁-antitrypsin (α₁-AT) is an important cause of early-onset severe panacinar pulmonary emphysema in adults in the 3rd and 4th decades of life and an important cause of liver disease in children (see Chapter 357.5). It is associated with panniculitis and vasculitis in adults.

### PATHOGENESIS

The type and concentration of α₁-AT are inherited as a series of codominant alleles on chromosomal segment 14q31-32.3. (See Chapter 357.5 for a discussion of genotypes and liver disease.) The autosomal recessive deficiency affects 1 in 1,600-2,500 people, or approximately 575,000 (estimated number of deficiency allele combinations) people in the United States, but is underdiagnosed. The highest risk for α₁-AT deficiency is found in whites, followed by Hispanics and Blacks, with the lowest prevalence among Mexican Americans, and little to no risk for Asians. Worldwide there are an estimated 116,000,000 carriers and 1,100,000 subjects with severe α₁-AT deficiency. The normal α₁-AT PiM protein is secreted by the liver into the circulation at a rate of approximately 34 mg/kg/day; it is also produced by lung epithelial cells and monocytes. Mutant protein is not produced (null) or is misfolded (PiZ and others); it can polymerize in the endoplasmic reticulum or be degraded, with subsequent low serum levels. Early adult-onset emphysema associated with α₁-AT deficiency occurs most commonly with PiZZ (mutation in SERPINA1 gene), although Pi (null) (null) and, to a lesser extent, other mutant Pi types such as SZ have been associated with emphysema.

α₁-AT and other serum antiproteases help inactivate proteolytic enzymes released from dead bacteria or leukocytes in the lung. Deficiency of these antiproteases leads to an accumulation of proteolytic enzymes in the lung, resulting in destruction of pulmonary tissue with subsequent development of emphysema. Furthermore, polymerized mutant protein in the lungs may be proinflammatory. The concentration of proteases (elastase) in the patients’ leukocytes may also be an important factor in determining the severity of clinical pulmonary disease with a given level of α₁-AT.

### CLINICAL MANIFESTATIONS

Most patients who have the PiZZ defect have little or no detectable pulmonary disease during childhood. A few have early onset of chronic pulmonary symptoms, including dyspnea, wheezing, and cough, and panacinar emphysema has been documented by lung biopsy; it is probable that these findings occur secondarily to infection, causing inflammation with consequent early disease. Smoking greatly increases the risk of emphysema in patients with mutant Pi types. Although newborn screening to identify children with PiZZ phenotype does not affect parental smoking habits, it does decrease smoking rates among affected adolescents.

Physical examination in childhood is usually normal. It very rarely reveals growth failure, an increased anteroposterior diameter of the chest with a hyperresonant percussion note, crackles if there is active infection, and clubbing. Severe emphysema can depress the diaphragm, making the liver and spleen more easily palpable.

### LABORATORY FINDINGS

Serum immunoassay measures low levels of α₁-AT; normal serum levels are 150-350 mg/dL. Serum electrophoresis reveals the pheno-
Chapter 393  \( \alpha_1 \)-Antitrypsin Deficiency and Emphysema

**Bibliography**


Bronchiolitis obliterans (BO), a chronic obstructive lung disease of the bronchioles and smaller airways, results from an insult to the lower respiratory tract leading to fibrosis of the small airways. In the non-transplant patient, BO most commonly occurs in the pediatric population after respiratory infections, particularly adenovirus (see Chapter 262), but also *Mycoplasma pneumoniae* (see Chapter 223), measles (see Chapter 246), *Legionella pneumophila* (see Chapter 208), influenza (see Chapter 258), and pertussis (see Chapter 197); other causes
include inflammatory diseases (juvenile idiopathic arthritis, systemic lupus erythematosus [see Chapter 158], scleroderma [see Chapter 160], Stevens-Johnson syndrome [see Chapter 152]), and inhalation of toxic fumes or particulate exposure (NO₂, incinerator fly ash, NH₃, diacetyl flavorings from microwave popcorn, papaverine, fiberglass) (Table 394-1).

Bronchiolitis obliterans syndrome (BOS), a clinical entity that relates to graft deterioration after transplantation as a result of progressive airway, is recognized as a long-term complication of lung and bone marrow transplantation; more than one-third of survivors of lung transplantation can develop this disorder. BOS occurs in all age groups, and the prevalence in 1 pediatric autopsy series was 2 per 1,000. The incidence of new cases appears to be decreasing. BOS appears to be more common in the southern hemisphere and among persons of Asian descent.

**PATHOGENESIS**

After the initial insult, inflammation affecting terminal bronchioles, respiratory bronchioles, and alveolar ducts can result in the obliteration of the airway lumen (Fig. 394-1). Epithelial damage resulting in abnormal repair is characteristic of BOS. Complete or partial obstruction of the airway lumen can result in air trapping or atelectasis. Bronchiolitis obliterans organizing pneumonia (BOOP) is a fibrosing lung disease that includes the histologic features of BO with extension of the inflammatory process from distal alveolar ducts into alveoli and proliferation of fibroblasts. BOS appears histologically similar to BO.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

Cough, fever, cyanosis, dyspnea, chest pain, and respiratory distress followed by initial improvement may be the initial signs of BO. In this phase, BO is easily confused with pneumonia, bronchitis, or bronchiolitis. Progression of the disease can ensue, with increasing dyspnea, chronic cough, sputum production, and wheezing. Physical examination findings are usually nonspecific and can include wheezing, hypoxemia, and crackles. Chest radiographs may be relatively normal compared with the extent of physical findings but can demonstrate hyperlucency and patchy infiltrates. Occasionally, a Swyer-James syndrome (unilateral hyperlucent lung; see Chapter 392) develops. Pulmonary function tests demonstrate variable findings but typically show signs of airway obstruction with a variable degree of bronchodilator response. Exercise testing shows reduced exercise capacity and impaired oxygen consumption. Ventilation–perfusion scans reveal a typical moth-eaten appearance of multiple matched defects in ventilation and perfusion. High-resolution chest CT often demonstrates patchy areas or a mosaic pattern of hyperlucency, air trapping, and bronchiectasis (Fig. 394-2). (Table 394-2 provides an overview of CT findings of BO and related disorders.) Physical and radiologic signs can wax and wane over weeks or months. Open lung biopsy or transbronchial biopsy remains the best means of establishing the diagnosis of BO or BOOP.

**TREATMENT**

No definitive therapy exists for BO. Administration of corticosteroids may be beneficial. Immunosuppressive agents, such as sirolimus, tacrolimus, aerosolized cyclosporine, hydroxychloroquine, and macrolide antibiotics, have been used in post–lung transplantation recipients with BO with variable success. Supportive measures with oxygen, antibiotics for secondary infections, and bronchodilators are adjunct therapies. The role of gastroesophageal reflex and its association with BO has been raised, with treatment suggested whenever the diagnosis is made. Azithromycin may be effective in patients with BOS. For BOOP, use of oral corticosteroids for up to 1 yr has been advocated as first-line therapy for symptomatic and progressive disease. Patients with asymptomatic or nonprogressive BOOP can be observed.

**PROGNOSIS**

Some patients with BO experience rapid deterioration in their condition and die within weeks of the initial symptoms; most nontransplant patients survive with chronic disability. BOS has a higher mortality...
Follicular bronchitis is a lymphoproliferative lung disorder characterized by the presence of lymphoid follicles alongside the airways (bronchi or bronchioles) and infiltration of the walls of bronchi and bronchioles. Although the cause is unknown, an infectious etiology (viral, \textit{L. pneumophila}; see Chapter 208) has been proposed. This disorder has been reported following lung transplant and in an HIV-positive child. It can occur in adults and children; in children, onset of symptoms generally occurs by 6 weeks of age and peaks between 6 and 18 months. Cough, moderate respiratory distress, fever, and fine crackles are common clinical findings. Fine crackles generally persist over time, and recurrence of symptoms is common. Chest radiographs may be relatively benign initially (air trapping, peribronchial thickening) but evolve into the typical interstitial pattern. Chest CT can show a fine reticular pattern as well as bronchiectasis and centrilobular branching but can also appear normal (see Table 394-2). Definitive diagnosis is made by open-lung biopsy (Fig. 394-3). Some patients with follicular bronchitis respond to therapy with corticosteroids. Prognosis is variable, with some patients having significant progression of pulmonary disease.

**Table 394-2** High-Resolution CT Patterns in Child with Interstitial Lung Disease

<table>
<thead>
<tr>
<th>STUDIES (N)</th>
<th>GROUND-GLASS OPACITY</th>
<th>THICK SEPTA</th>
<th>NODULES</th>
<th>MOSAIC PATTERN</th>
<th>HONEYCOMBING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis obliterans</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>X</td>
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<tr>
<td>Nonspecific interstitial pneumonitis</td>
<td>6</td>
<td>X</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonitis</td>
<td>4</td>
<td>X</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Follicular bronchitis or neuroendocrine cell hyperplasia of infancy</td>
<td>4</td>
<td>X</td>
<td>—</td>
<td>—</td>
<td>X</td>
</tr>
<tr>
<td>Lymphocytic interstitial pneumonitis</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>X</td>
<td>—</td>
</tr>
<tr>
<td>Lymphangiomatosis</td>
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<td>—</td>
<td>X</td>
<td>—</td>
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<tr>
<td>Lymphangiectasia</td>
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<td>—</td>
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<tr>
<td>Pulmonary alveolar proteinosis</td>
<td>2</td>
<td>X</td>
<td>X</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>


**Figure 394-2** High-resolution CT scan of the chest of a child with bronchiolitis obliterans demonstrating mosaic perfusion and vascular attenuation. Air-trapping is demonstrated by lack of increase in attention or decrease in lung volume in dependent lung. (Image courtesy of Alan Brody, MD, Cincinnati Children’s Hospital Medical Center, Ohio.)

**Figure 394-3** Follicular bronchiolitis in a 3 yr old girl with mosaic attenuation and cylindrical bronchiectasis. CT findings suggested BO, but a biopsy documented the presence of follicular bronchiolitis. (From Long FR, Druhan SM, Kuhn JP. Diseases of the bronchi and pulmonary aeration. In Slovis TL, editor: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 73-71.)

394.2 Follicular Bronchitis

Steven R. Boas

Follicular bronchitis is a lymphoproliferative lung disorder characterized by the presence of lymphoid follicles alongside the airways (bronchi or bronchioles) and infiltration of the walls of bronchi and bronchioles. Although the cause is unknown, an infectious etiology (viral, \textit{L. pneumophila}; see Chapter 208) has been proposed. This disorder has been reported following lung transplant and in an HIV-positive child. It can occur in adults and children; in children, onset of symptoms generally occurs by 6 wk of age and peaks between 6 and 18 mo. Cough, moderate respiratory distress, fever, and fine crackles are common clinical findings. Fine crackles generally persist over time, and recurrence of symptoms is common. Chest radiographs may be relatively benign initially (air trapping, peribronchial thickening) but evolve into the typical interstitial pattern. Chest CT can show a fine reticular pattern as well as bronchiectasis and centrilobular branching but can also appear normal (see Table 394-2). Definitive diagnosis is made by open-lung biopsy (Fig. 394-3). Some patients with follicular bronchitis respond to therapy with corticosteroids. Prognosis is variable, with some patients having significant progression of pulmonary disease.
Bibliography


Pulmonary alveolar microlithiasis (PAM) is a rare disease characterized by the formation of lamellar concretions of calcium phosphate or “microliths” within the alveoli, creating a classic pattern on the radiograph (Fig. 394-4).

**EPIDEMIOLOGY AND ETIOLOGY**

Although the mean age at time of diagnosis is in the mid 30s, the onset of the disease can occur in childhood. PAM is inherited in an autosomal recessive pattern. In 2006, a mutation in the gene that encodes for the type IIb sodium-phosphate cotransporter protein (SCL34A2) was discovered in people with PAM. This gene is expressed in high levels in the lungs predominantly in type 2 epithelial cells. While the precise role of this protein is unknown, it is speculated that it helps remove phosphate from the alveolar space as well as a phosphate regular in other organs.

In some families, progression of disease is rapid. An equal male and female incidence is noted. Although PAM is found throughout the world, there is a high incidence in Turkey and a lesser incidence in Italy, Japan, and India.

**CLINICAL MANIFESTATIONS**

When symptomatic, patients with PAM usually complain of dyspnea on exertion and nonproductive cough. Physical examination of the lungs can reveal fine inspiratory crackles and diminished breath sounds. Clubbing occurs, although this is usually a more advanced sign. Discordance between the clinical and radiographic manifestations is common. Many children are often asymptomatic on initial presentation and present with symptoms during adulthood. Complications of pneumothorax, pleural adhesions and calcifications, pleural fibrosis, apical bullae, and extrapulmonary sites of microliths have been reported (kidneys, prostate, sympathetic chain, and testes).

**DIAGNOSIS**

Chest radiography typically reveals bilateral infiltrates with a fine micronodular appearance or sandstorm appearance with greater density in the lower and middle lung fields (see Fig. 394-4). CT of the chest shows diffuse micronodular calcified densities, with thickening of the microliths along the septa and around distal bronchioles, especially in the inferior and posterior regions (see Table 394-2). Diffuse uptake of technetium-99 methylene diphosphonate by nuclear scan has been reported. Open lung and transbronchial lung biopsy reveal 0.1-0.3 mm laminated calcific concretions within the alveoli. Although the alveoli are often normal initially, progression to pulmonary fibrosis with advancing disease usually ensues. Sputum expectoration might reveal small microliths, although this finding is not diagnostic for PAM and is not typically seen in children. Detection of calcium deposits in bronchoalveolar lavage fluid on bronchoscopy supports the diagnosis. Pulmonary function testing reveals restrictive lung disease with impaired diffusing capacity as the disease progresses, whereas exercise testing demonstrates arterial oxygen desaturation. Detection of a mutation in the SCL34A2 gene confirms the diagnosis. The differential diagnosis includes sarcoidosis, miliary tuberculosis, hemosiderosis, healed disseminated histoplasmosis, pulmonary calcinosis, and metastatic pulmonary calcifications.

**TREATMENT**

No specific treatment is effective, although some clinicians have used glucocorticosteroids, etidronate disodium, and bronchopulmonary lavage with limited success. Lung transplantation has been performed for this condition, although it is unknown whether the disease recurs after transplantation.

**PROGNOSIS**

Progressive cardiopulmonary disease can ensue, leading to cor pulmonale, superimposed infections, and subsequent death in mid-adulthood. Because of the familial nature of this disease, counseling and chest radiographs of family members are indicated.
Bibliography


Chapter 395

Congenital Disorders of the Lung

395.1 Pulmonary Agenesis and Aplasia  
Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

Pulmonary agenesis differs from hypoplasia in that agenesis entails the complete absence of a lung. Agenesis differs from aplasia by the absence of a bronchial stump or carina that is seen in aplasia. Bilateral pulmonary agenesis is incompatible with life, manifesting as severe respiratory distress and failure. Pulmonary agenesis is thought to be an autosomal recessive trait, with an estimated incidence of 1 in 10,000-15,000 births.

CLINICAL MANIFESTATIONS AND PROGNOSIS

Unilateral agenesis or hypoplasia can have few symptoms and nonspecific findings, resulting in only 33% of the cases being diagnosed while the patient is living. Symptoms tend to associated with central airway complications of compression, stenosis, and/or tracheobronchomalacia. In patients in whom the right lung is absent, the aorta can compress the trachea and lead to symptoms of central airway compression. Right lung agenesis has a higher morbidity and mortality than left lung agenesis. Pulmonary agenesis is often seen in association with other congenital anomalies such as the VACTERL sequence (vertebral anomalies, anal atresia, congenital heart disease, tracheoesophageal fistula, renal anomalies, and limb anomalies), ipsilateral facial and skeletal malformations, and central nervous system and cardiac malformations. Compensatory growth of the remaining lung allows improved gas exchange, but the mediastinal shift can lead to scoliosis and airway compression. Scoliosis can result from unequal thoracic growth.

DIAGNOSIS AND TREATMENT

Chest radiographic findings of unilateral lung or lobar collapse with a shift of mediastinal structures toward the affected side can prompt referral for suspected foreign-body aspiration, mucous plug occlusion, or other bronchial mass lesions. The diagnosis requires a high index of suspicion to avoid the unnecessary risks of bronchoscopy, including potential perforation of the rudimentary bronchus. CT of the chest is diagnostic, although the diagnosis may be suggested by chronic changes in the contralateral aspect of the chest wall and lung expansion on chest radiographs. Because pulmonary agenesis can be associated with a wide variety of congenital lesions, whole-body MRI can be useful to determine whether other systems (e.g., cardiac, gastrointestinal) are affected. Conservative treatment is usually recommended, although surgery has offered benefit in selected cases.

395.2 Pulmonary Hypoplasia  
Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

Pulmonary hypoplasia involves a decrease in both the number of alveoli and the number of airway generations. The hypoplasia may be bilateral in the setting of bilateral lung constraint, as in oligohydramnios or thoracic dystrophy. Pulmonary hypoplasia is usually secondary to other intrauterine disorders that produce an impairment of normal lung development (see Chapter 101). Conditions such as deformities of the thoracic spine and rib cage (thoracic dystrophy), pleural effusions with fetal hydrops, congenital pulmonary airway malformation, and congenital diaphragmatic hernia physically constrain the developing lung. Any condition that produces oligohydramnios (fetal renal insufficiency or prolonged premature rupture of membranes) can also lead to diminished lung growth. In these conditions, airway and arterial branching are inhibited, thereby limiting the capillary surface area. Large unilateral lesions, such as congenital diaphragmatic hernia or pulmonary airway malformation, can displace the mediastinum and thereby produce a contralateral hypoplasia, although usually not as severe as that seen on the ipsilateral side.

CLINICAL MANIFESTATIONS

Pulmonary hypoplasia is usually recognized in the newborn period, owing to either the respiratory insufficiency or the presentation of persistent pulmonary hypertension (see Chapter 101.7). Later presentation (tachypnea) with stress or respiratory viral infection can be seen in infants with mild pulmonary hypoplasia.

DIAGNOSIS AND TREATMENT

A variety of imaging techniques, including MRI and ultrasound, with estimation of oligohydramnios, can be helpful to identify hypoplasia, but not to predict pulmonary function. Mechanical ventilation and oxygen may be required to support gas exchange. Specific therapy to control associated pulmonary hypertension, such as inhaled nitric oxide, may be useful. In cases of severe hypoplasia, the limited capacity of the lung for gas exchange may be inadequate to sustain life. Extra-corpeal membrane oxygenation can provide gas exchange for a critical period of time and permit survival. Rib-expanding devices (vertically expandable prosthetic titanium ribs) can improve the survival of patients with thoracic dystrophies (see Chapter 700).

Bibliography is available at Expert Consult.

395.3 Congenital Cystic Malformation  
Joshua A. Blatter and Jonathan D. Finder

PATHOLOGY

Congenital pulmonary airway malformation (CPAM), formerly known as cystic adenomatoid malformation, consists of hamartomatous or dysplastic lung tissue mixed with more normal lung, generally confined to 1 lobe. This congenital pulmonary disorder occurs in approximately 1-4 in 100,000 births. Prenatal ultrasonographic findings are classified as macrocystic (single or multiple cysts >5 mm) or microcystic (echocystic cysts <5 mm). Five histologic patterns have been described. Type 0 (acinar dysplasia) is least common (<3%) and consists of microcystic disease throughout the lungs. The prognosis is poorest for this type, and infants die at birth. Type 1 (60%) is macrocystic and consists of a single or several large (>2 cm in diameter) cysts lined with ciliated pseudostratified epithelium; the lesion is localized involving only a part of 1 lobe. One-third of cases have mucus-secreting cells. Presentation is in utero or in the newborn period. Cartilage is rarely seen in the wall of the cyst. This type has a good prognosis for survival. Type 2 (20%) is microcystic and consists of multiple small cysts with histology similar to that of the type 1 lesion. Type 2 is associated with other serious congenital anomalies (renal, cardiac, diaphragmatic hernia) and carries a poor prognosis. Type 3 (<10%) is seen mostly in males; the lesion is a mixture of microcysts and solid tissue with bronchiole-like structures lined with cuboidal ciliated epithelium and separated by areas of nonciliated cuboidal epithelium. The prognosis for this type, like type 0, is poor. Type 4 (10%) is commonly macrocystic and lacks mucus cells. It is associated with malignancy.
Bibliography
Bibliography

Part XIX  Respiratory System

Respiratory System (Fig. 395-2). Occasionally, an air–fluid level suggests a lung abscess (see Chapter 402).

TREATMENT
Antenatal intervention in severely affected infants is controversial but can include excision of the affected lobe for microcystic lesions, aspiration of macrocystic lesions, and, rarely, open fetal surgery. In the postnatal period, surgery is indicated for symptomatic patients. Although surgery may be delayed for asymptomatic infants because postnatal resolution has been reported, true resolution appears to be very rare in that abnormalities usually remain detectable on CT or MRI. Sarcomatous and carcinomatous degeneration have been described in patients with CPAM, so surgical resection by 1 year of age is recommended to limit malignant potential. The mortality rate is <10%.

Another indication for surgery is to rule out pleuropulmonary (pleuropulmonary blastoma) and can present either in childhood or in asymptomatic adults.

ETIOLOGY
The lesion probably results from an embryologic injury before the 35th day of gestation, with maldevelopment of terminal bronchiolar structures. Histologic examination reveals little normal lung and many glandular elements. Cysts are very common; cartilage is rare. The presence of cartilage might indicate a somewhat later embryologic insult, perhaps extending into the 10th-24th wk. Although growth factor interactions and signaling mechanisms have been implicated in altered lung-branching morphogenesis, the exact roles in the maldevelopment seen here remain obscure.

DIAGNOSIS
Cystic airway malformations can be diagnosed in utero by ultrasonography (Fig. 395-1). Fetal cystic lung abnormalities can include CPAM (40%), pulmonary sequestration (14%) (see Chapter 395.4), or both (26%); the median age at diagnosis is usually 21 wk gestation. In 1 series, only 7% had severe signs of fetal distress including hydrops, pleural effusion, polyhydramnios, ascites, or severe facial edema; 96% of the fetuses were born alive, 2 of whom died in the neonatal period. Lesions causing fetal hydrops have a poor prognosis. Large lesions, by compressing adjacent lung, can produce pulmonary hypoplasia in non-affected lobes (see Chapter 395.2). Even lesions that appear large in early gestation can regress considerably or decrease in relative size and be associated with good pulmonary function in childhood. CT allows accurate diagnosis and sizing of the lesion and is indicated even in asymptomatic neonates.

CLINICAL MANIFESTATIONS
Patients can present in the newborn period or early infancy with respiratory distress, recurrent respiratory infection, and pneumothorax. The lesion may be confused with a diaphragmatic hernia (see Chapter 101.8). Patients with smaller lesions are usually asymptomatic until mid-childhood, when episodes of recurrent or persistent pulmonary infection or chest pain occur. Breath sounds may be diminished, with mediastinal shift away from the lesion on physical examination. Chest radiographs reveal a cystic mass, sometimes with mediastinal shift

Figure 395-1 Imaging of congenital pulmonary airway malformation of the lung (CPAM) on the same patient with prenatal ultrasound scan (A), chest radiograph (B), and CT scan (C). Note that the lesion is not visible on the chest radiograph. (From Lakhoo K: Management of congenital cystic adenomatous malformations of the lung, Arch Dis Child Fetal Neonatal Ed 94:F73–F76, 2009.)

Figure 395-2 Neonatal chest x-ray showing large multicystic mass in the left hemithorax with mediastinal shift as a result of congenital pulmonary airway malformation (CPAM). (From Williams HJ, Johnson KJ: Imaging of congenital cystic lung lesions, Paediatr Respir Rev 3:120–127, 2002.)

(Fig. 395-2). Occasionally, an air–fluid level suggests a lung abscess (see Chapter 402).

TREATMENT
Antenatal intervention in severely affected infants is controversial but can include excision of the affected lobe for microcystic lesions, aspiration of macrocystic lesions, and, rarely, open fetal surgery. In the postnatal period, surgery is indicated for symptomatic patients. Although surgery may be delayed for asymptomatic infants because postnatal resolution has been reported, true resolution appears to be very rare in that abnormalities usually remain detectable on CT or MRI. Sarcomatous and carcinomatous degeneration have been described in patients with CPAM, so surgical resection by 1 year of age is recommended to limit malignant potential. The mortality rate is <10%. Another indication for surgery is to rule out pleuropulmonary
Pulmonary sequestration is a congenital anomaly of lung development that can be intrapulmonary or extrapulmonary, according to the location within the visceral pleura. The majority of sequestrations are intrapulmonary.

PATHOPHYSIOLOGY

The lung tissue in a sequestration does not connect to a bronchus and receives its arterial supply from the systemic arteries (commonly off the aorta) and returns its venous blood to the right side of the heart through the inferior vena cava (extralobar) or pulmonary veins (intralobar). The sequestration functions as a space-occupying lesion within the chest; it does not participate in gas exchange and does not lead to a left-to-right shunt or alveolar dead space. Communication with the airway can occur as the result of rupture of infected material into an adjacent airway. Collateral ventilation within intrapulmonary lesions via pores of Kohn can occur. Pulmonary sequestrations can arise through the same pathoembryologic mechanism as a remnant of a diverticular outgrowth of the esophagus. Some propose that intrapulmonary sequestration is an acquired lesion primarily caused by infection and inflammation; inflammation leads to cystic changes and hypertrophy of a feeding systemic artery. This is consistent with the rarity of this lesion in autopsy series of newborns. Gastric or pancreatic tissue may be found within the sequestration. Cysts also may be present. Other associated congenital anomalies, including CPAM (see Chapter 395.3), diaphragmatic hernia (see Chapter 101.8), and esophageal cysts, are not uncommon. Some believe that intrapulmonary sequestration is often a manifestation of CPAM and have questioned the existence of intrapulmonary sequestration as a separate entity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Physical findings in patients with sequestration include an area of dullness to percussion and decreased breath sounds over the lesion. During infection, crackles may also be present. A continuous or purely systolic murmur may be heard over the back. If findings on routine chest radiographs are consistent with the diagnosis, further delineation is indicated before surgical intervention (Fig. 395-3). CT with contrast can demonstrate both the extent of the lesion and its vascular supply. MR angiography is also useful. Ultrasonography can help rule out a diaphragmatic hernia and demonstrate the systemic artery. Surgical removal is recommended. Identifying the blood supply before surgery avoids inadvertently severing its systemic artery. Coil embolization (transumbilical in neonates; arterial in older patients) has been successful in treating patients with sequestration.

Intrapulmonary sequestration is generally found in a lower lobe and does not have its own pleura. Patients usually present with infection. In older patients, hemoptyysis is common. A chest radiograph during a period when there is no active infection reveals a mass lesion; an air-fluid level may be present. During infection, the margins of the lesion may be blurred. There is no difference in the incidence of this lesion in each lung.

Extrapulmonary sequestration is much more common in boys, and almost always involves the left lung. This lesion is enveloped by a pleural covering and is associated with diaphragmatic hernia and other abnormalities such as colonic duplication, vertebral abnormalities, and pulmonary hypoplasia. Many of these patients are asymptomatic when the mass is discovered by routine chest radiography. Other patients present with respiratory symptoms or heart failure. Subdiaphragmatic extrapulmonary sequestration can manifest as an abdominal mass on prenatal ultrasonography. The advent of prenatal ultrasonography has also enabled evidence that fetal pulmonary sequestrations can spontaneously regress.

TREATMENT

Treatment of intrapulmonary sequestration is surgical removal of the lesion, a procedure that usually requires excision of the entire involved lobe. Segmental resection occasionally suffices. Surgical resection of the involved area is recommended for extrapulmonary sequestration. Coil embolization of the feeding artery has also been successful.

ETIOLOGY AND PATHOLOGY

Bronchogenic cysts arise from abnormal budding of the tracheal diverticulum of the foregut before the 16th wk of gestation and are originally lined with ciliated epithelium. They are more commonly found on the right and near a midline structure (trachea, esophagus, carina), but peripheral lower lobe and perihilar intrapulmonary cysts are not...
Bibliography

Bibliography
Congenital Pulmonary Lymphangiectasia

Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

Congenital pulmonary lymphangiectasia is characterized by greatly dilated lymphatic ducts throughout the lung. It can occur in 3 pathologic circumstances: pulmonary venous obstruction that produces an elevated transvascular pressure and engorges the pulmonary lymphatics; generalized lymphangiectasia, as a generalized disease of several organ systems, including lungs and the intestines (can be associated with Noonan syndrome); and primary lymphangiectasia limited to the lung as a manifestation of an abnormality in lymphatic development.

CLINICAL MANIFESTATIONS AND TREATMENT

Children with pulmonary venous obstruction or severe pulmonary lymphangiectasia present with dyspnea and cyanosis in the newborn period. Hydrops fetalis may be diagnosed antenatally. Chest radiographs reveal diffuse, dense, reticular densities with prominence of Kerley B lines. Pleural effusions are common; thoracentesis will reveal chylothorax in this setting. If the lung is not completely involved, the spared areas appear hyperlucent. Respiration is compromised because of impaired diffusion and decreased pulmonary compliance. The diagnosis can be suggested by CT scan and/or cardiac catheterization; definitive diagnosis requires lung biopsy (either thoracoscopic or open).

Treatment is supportive and includes administration of oxygen, mechanical ventilation, nutritional support (including gastrostomy placement and use of feedings containing medium-chain triglycerides), and careful fluid management with diuretics. Primary pulmonary lymphangiectasia can produce severe pulmonary dysfunction that can require long-term mechanical ventilation; long-term survival and resolution of respiratory insufficiency is possible even in severe cases. Occasionally, the pulmonary venous obstruction is secondary to left-sided cardiac lesions; relief of the latter can produce improvement in pulmonary dysfunction. Generalized lymphangiectasia produces milder pulmonary dysfunction, and survival to mid-childhood and beyond is not unusual.

Bibliography is available at Expert Consult.

395.7 Lung Hernia

Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

A lung hernia is a protrusion of the lung beyond its normal thoracic boundaries. Approximately 20% are congenital, with the remainder being noted after chest trauma or thoracic surgery or in patients with pulmonary diseases such as cystic fibrosis (see Chapter 403) or asthma (see Chapter 144), which cause frequent cough and generate high intrathoracic pressure. A congenital weakness of the suprapleural membrane (Sibson fascia) or musculature of the neck can play a role in the appearance of a lung hernia. More than half of congenital lung hernias and almost all acquired hernias are cervical. Congenital cervical hernias usually occur anteriorly through a gap between the scalenus anterior and sternocleidomastoid muscles. Cervical herniation is usually prevented by the trapezius muscle (posteriorly, at the thoracic inlet) and by the 3 scalene muscles (laterally).

CLINICAL MANIFESTATIONS AND TREATMENT

The presenting sign of a cervical hernia (Sibson hernia) is usually a neck mass noticed while straining or coughing. Some lesions are asymptomatic and detected only when a chest film is taken for another reason. Findings on physical examination are normal except during Valsalva maneuver, when a soft bulge may be noticed in the neck. In most cases, no treatment is necessary, although these hernias can cause problems during attempts to place a central venous catheter through the jugular or subclavian veins. They can resolve spontaneously. Paravertebral or parasternal hernias are usually associated with rib anomalies. Intercostal hernias usually occur parasternally, where the external intercostal muscle is absent. Posteriorly, despite the seemingly inadequate internal intercostal muscle, the paraspinal muscles usually prevent herniation. Straining, coughing, or playing a musical...
Bibliography
Bibliography
instrument can have a role in causing intercostal hernias, but in most cases, there is probably a preexisting defect in the thoracic wall. Surgical treatment for lung hernia is occasionally justified for cosmetic reasons. In patients with severe chronic pulmonary disease and chronic cough and for whom cough suppression is contraindicated, permanent correction might not be achieved.

Bibliography is available at Expert Consult.

395.8 Other Congenital Malformations of the Lung

Joshua A. Blatter and Jonathan D. Finder

CONGENITAL LOBAR EMPHYSEMA AND PULMONARY CYSTS
See Chapter 392.

PULMONARY ARTERIOVENOUS MALFORMATION
See Chapters 432 and 444.

BRONCHOBILIARY FISTULA
A bronchoiliary fistula consists of a fistulous connection between the right middle lobe bronchus and the left hepatic ductal system. Although diagnosis can be delayed until adulthood, this rare anomaly typically manifests with life-threatening bronchopulmonary infections in early infancy. Girls are more commonly affected. Definitive diagnosis requires endoscopy or exploratory surgery. Treatment includes surgical excision of the entire intrathoracic portion of the fistula. If the hepatic portion of the fistula does not communicate with the biliary system or duodenum, the involved segment might also have to be resected. Bronchoiliary communications also occur as acquired lesions resulting from hepatic disease complicated by infection.

Bibliography is available at Expert Consult.
Bibliography
Bibliography
A sequela of several different pathologic processes, pulmonary edema is an excessive accumulation of fluid in the interstitium and air spaces of the lung resulting in oxygen desaturation, decreased lung compliance, and respiratory distress. The condition is common in the acutely ill child.

**PATHOPHYSIOLOGY**

Although pulmonary edema is traditionally separated into two categories according to cause (cardiogenic and noncardiogenic), the end result of both processes is a net fluid accumulation within the interstitial and alveolar spaces. Noncardiogenic pulmonary edema, in its most severe state, is also known as **acute respiratory distress syndrome** (see Chapters 71 and 373).

The hydrostatic pressure and colloid osmotic (oncotic) pressure on either side of a pulmonary vascular wall, along with vascular permeability, are the forces and physical factors that determine fluid movement through the vessel wall. Baseline conditions lead to a net filtration of fluid from the intravascular space into the interstitium. This "extra" interstitial fluid is usually rapidly reabsorbed by pulmonary lymphatics. Conditions that lead to altered vascular permeability, increased pulmonary vascular pressure, and decreased intravascular oncotic pressure increase the net flow of fluid out of the vessel (Table 396-1). Once the capacity of the lymphatics for fluid removal is exceeded, water accumulates in the lung.

To understand the sequence of lung water accumulation, it is helpful to consider its distribution among 4 distinct compartments, as follows:

- **Vascular compartment:** This compartment consists of all blood vessels that participate in fluid exchange with the interstitium. The vascular compartment is separated from the interstitium by capillary endothelial cells. Several endogenous inflammatory mediators, as well as exogenous toxins, are implicated in the pathogenesis of pulmonary capillary endothelial damage, leading to the "leakiness" seen in several systemic processes.

- **Interstitial compartment:** The importance of this space lies in its interposition between the alveolar and vascular compartments. As fluid leaves the vascular compartment, it collects in the interstitium before overflowing into the air spaces of the alveolar compartment.

- **Alveolar compartment:** This compartment is lined with type 1 and type 2 epithelial cells. These epithelial cells have a role in active fluid transport from the alveolar space, and they act as a barrier to exclude fluid from the alveolar space. The potential fluid volume of the alveolar compartment is many times greater than that of the interstitial space, perhaps providing another reason that alveolar edema clears more slowly than interstitial edema.

---

**Table 396-1**  
**Etiology of Pulmonary Edema**

| **INCREASED PULMONARY CAPILLARY PRESSURE** |  
| Cardiogenic, such as left ventricular failure  
| Noncardiogenic, as in pulmonary venoocclusive disease, pulmonary venous fibrosis, mediastinal tumors  
| **INCREASED CAPILLARY PERMEABILITY** |  
| Bacterial and viral pneumonia  
| Acute respiratory distress syndrome  
| Inhaled toxic agents  
| Circulating toxins  
| Vasactive substances such as histamine, leukotrienes, thromboxanes  
| Diffuse capillary leak syndrome, as in sepsis  
| Immunologic reactions, such as transfusion reactions  
| Smoke inhalation  
| Aspiration pneumonia/pneumonitis  
| Drowning and near drowning  
| Radiation pneumonitis  
| Uremia  
| **LYMPHATIC INSUFFICIENCY** |  
| Congenital and acquired  
| **DECREASED ONCOTIC PRESSURE** |  
| Hypoalbuminemia, as in renal and hepatic diseases, protein-losing states, and malnutrition  
| **INCREASED NEGATIVE INTERSTITIAL PRESSURE** |  
| Upper airway obstructive lesions, such as croup and epiglottitis  
| Reexpansion pulmonary edema  
| **MIXED OR UNKNOWN CAUSES** |  
| Neurogenic pulmonary edema  
| High-altitude pulmonary edema  
| Eclampsia  
| Pancreatitis  
| Pulmonary embolism  
| Heroin (narcotic) pulmonary edema  

Pulmonary lymphatic compartment: There is an extensive network of pulmonary lymphatics. Excess fluid present in the alveolar and interstitial compartments is drained via the lymphatic system. When the capacity for drainage of the lymphatics is surpassed, fluid accumulation occurs.

ETIOLOGY
The specific clinical findings vary according to the underlying mechanism (see Table 396-1). Transudation of fluid as a result of increased pulmonary vascular pressure (capillary hydrostatic pressure) occurs in several cardiac processes. A significant left-to-right shunting lesion, such as a septal defect, leads to a pressure and volume load on the pulmonary vasculature. The resultant pulmonary edema is one of the hallmarks of congestive heart failure. Left ventricular failure, mitral valve disease, and pulmonary venous obstructive lesions cause increased "backpressure" in the pulmonary vasculature. This results in an increase in pulmonary capillary pressure.

Increased capillary permeability is usually secondary to endothelial damage. Such damage can occur secondary to direct injury to the alveolar epithelium or indirectly through systemic processes that deliver circulating inflammatory mediators or toxins to the lung. Inflammatory mediators (tumor necrosis factor, leukotrienes, thromboxanes), and vasoactive agents (nitric oxide, histamine) formed during pulmonary and systemic processes potentiate the altered capillary permeability that occurs in many disease processes, with sepsis being a common cause.

Fluid homeostasis in the lung largely depends on drainage via the lymphatics. Experimentally, pulmonary edema occurs with obstruction of the lymphatic system. Increased lymph flow and dilatation of lymphatic vessels occur in chronic edematous states.

A decrease in intravascular oncotic pressure leads to pulmonary edema by altering the forces promoting fluid reentry into the vascular space. This occurs in dilutional disorders, such as fluid overload with hypotonic solutions, and in protein-losing states, such as nephrotic syndrome and malnutrition.

The excessive negative interstitial pressure seen in upper airway diseases, such as croup and laryngospasm, may promote pulmonary edema. Aside from the physical forces present in these diseases, other mechanisms may also be involved. Theories implicating an increase in CO₂ tension, decreased O₂ tension, and extreme increases in cardiac afterload, leading to transient cardiac insufficiency.

The mechanism causing neurogenic pulmonary edema is not clear. A massive sympathetic discharge secondary to a cerebral injury may produce increased pulmonary and systemic vasoconstriction, resulting in a shift of blood to the pulmonary vasculature, an increase in capillary pressure, and edema formation. Inflammatory mechanisms may also play a role in increasing capillary permeability.

The mechanism responsible for high-altitude pulmonary edema is unclear, but it may also be related to sympathetic outflow, increased pulmonary vascular pressures, and hypoxia-induced increases in capillary permeability (see Chapter 73).

Active ion transport followed by passive, osmotic water movement is important in clearing the alveolar space of fluid. There are some experimental data that β agonists and growth factors increase alveolar fluid removal. Interindividual genetic differences in the rates of these transport processes may be important in determining which individuals are susceptible to altitude-related pulmonary edema. Although the existence of these mechanisms suggests that therapeutic interventions may be developed to promote resolution of pulmonary edema, no such therapies currently exist.

CLINICAL MANIFESTATIONS
The clinical features depend on the mechanism of edema formation. In general, interstitial edema and alveolar edema prevent the inflation of alveoli, leading to atelectasis and decreased surfactant production. This results in diminished pulmonary compliance and tidal volume. The patient must increase respiratory effort and/or the respiratory rate so as to maintain minute ventilation. The earliest clinical signs of pulmonary edema include increased work of breathing, tachypnea, and dyspnea. As fluid accumulates in the alveolar space, auscultation reveals fine crackles and wheezing, especially in dependent lung fields. In cardiogenic pulmonary edema, a gallop may be present as well as peripheral edema and jugular venous distention.

Chest radiographs can provide useful ancillary data, although findings of initial radiographs may be normal. Early radiographic signs that represent accumulation of interstitial edema include peribronchial and perivascular cuffing. Diffuse streakiness reflects interlobular edema and distended pulmonary lymphatics. Diffuse, patchy densities, the so-called butterfly pattern, represent bilateral interstitial or alveolar infiltrates and are a late sign. Cardiomegaly is often seen with cardiogenic causes of pulmonary edema. Heart size is usually normal in noncardiogenic pulmonary edema (Table 396-2). Chest tomography demonstrates edema accumulation in the dependent areas of the lung. As a result, changing the patient’s position can alter regional differences in lung compliance and alveolar ventilation.

Measurement of brain natriuretic peptide, often elevated in heart disease, can help differentiate cardiac from pulmonary causes of pulmonary edema. A brain natriuretic peptide level >500 pg/mL suggests heart disease; a level <100 pg/mL suggests lung disease.

TREATMENT
The treatment of a patient with noncardiogenic pulmonary edema is largely supportive, with the primary goal to ensure adequate ventilation and oxygenation. Additional therapy is directed toward the underlying cause. Patients should receive supplemental oxygen to increase alveolar oxygen tension and pulmonary vasodilation. Patients with pulmonary edema of cardiogenic causes should be managed with diuretics, inotropic agents and systemic vasodilators to reduce left ventricular afterload (see Chapter 442). Diuretics are also valuable in the treatment of pulmonary edema associated with total body fluid overload (sepsis, renal insufficiency). Morphine is often helpful as a vasodilator and a mild sedative.

Positive airway pressure improves gas exchange in patients with pulmonary edema. In tracheally intubated patients, positive end-expiratory pressure can be used to optimize pulmonary mechanics. Noninvasive forms of ventilation, such as mask or nasal prong
continuous positive airway pressure, are also effective. The mechanism by which positive airway pressure improves pulmonary edema is not entirely clear but is not associated with decreasing lung water. Rather, continuous positive airway pressure prevents complete closure of alveoli at the low lung volumes present at the end of expiration. It may also recruit already collapsed alveolar units. This leads to increased functional residual capacity and improved pulmonary compliance, improved surfactant function, and decreased pulmonary vascular resistance. The net effect is to decrease the work of breathing, improve oxygenation, and decrease cardiac afterload.

When mechanical ventilation becomes necessary, especially in non-cardiogenic pulmonary edema, care must be taken to minimize the risk of development of complications from barotrauma, including pneumothorax, pneumomediastinum, and primary alveolar damage (see Chapter 71.1). Lung protective strategies include setting low tidal volumes, relatively high positive end-expiratory pressure, and allowing for permissive hypercapnia.

High-altitude pulmonary edema should be managed with altitude descent and supplemental oxygen. Portable continuous positive airway pressure or a portable hyperbaric chamber is also helpful. Nifedipine (10 mg initially, and then 20-30 mg by slow release every 12-24 hr) in adults is also helpful. If there is a history of high-altitude pulmonary edema, nifedipine and β-adrenergic agonists (inhaled) may prevent recurrence (see Chapter 73).

_Bibliography is available at Expert Consult._
Bibliography


correlates with increasing infiltrates on chest radiographs. These infiltrations, mucosal sloughing, and alveolar consolidation that often rapidly after massive aspiration. These occur earlier, become more atelectasis, intravascular fluid shifts, and pulmonary edema all occur 0.8 mL/kg and/or pH ≤ 2.5. Hypoxemia, hemorrhagic pneumonitis, atelectasis, intravascular fluid shifts, and pulmonary edema all occur rapidly after massive aspiration. These occur earlier, become more severe, and last longer with acid aspiration. Most clinical changes are present within minutes to 1-2 hr after the aspiration event. In the next 24-48 hr, there is a marked increase in lung parenchymal neutrophil infiltrations, mucosal sloughing, and alveolar consolidation that often correlates with increasing infiltrates on chest radiographs. These changes tend to occur significantly later and are more prolonged after aspiration of particulate material. Although infection usually does not have a role in initial lung injury after aspiration of gastric contents, aspiration may impair pulmonary defenses, predisposing the patient to secondary bacterial pneumonia. In the patient who has shown clinical improvement but then demonstrates clinical worsening, especially with fever and leukocytosis, secondary bacterial pneumonia should be suspected.

Treatment
If large-volume or highly toxic substance aspiration occurs in a patient who already has an artificial airway in place, it is important to perform immediate suctioning of the airway. If immediate suctioning cannot be performed, later suctioning or bronchoscopy is usually of limited therapeutic value except when there is suspicion of significant particulate aspiration. Attempts at acid neutralization are not warranted because acid is rapidly neutralized by the respiratory epithelium. Patients in whom large-volume or toxic aspiration is suspected should be observed, should undergo oxygenation measurement by oximetry or blood gas analysis, and should undergo a chest radiograph, even if they are asymptomatic. If the chest radiograph findings and oxygen saturation are normal, and the patient remains asymptomatic, home observation, after a period of observation in the hospital or office, is adequate. No treatment is indicated at that time, but the caregivers should be instructed to bring the child back in for medical attention should respiratory symptoms or fever develop. For patients who present with abnormal findings or in whom such findings develop during observation, oxygen therapy is given to correct hypoxemia. Endotracheal intubation and mechanical ventilation are often necessary for more severe cases. Bronchodiators may be tried, although they are usually of limited benefit. Animal studies indicate that treatment with corticosteroids does not provide benefit, unless given nearly simultaneously with the aspiration event; use of these agents may increase the risk of secondary infection. Prophylactic antibiotics are not indicated, although in the patient with limited reserve, early antibiotic coverage may be appropriate. If used, antibiotics that cover for anaerobic microbes should be considered. If the aspiration event occurs in a hospitalized or chronically ill patient, coverage of Pseudomonas, Staphylococcus aureus, and enteric Gram-negative organisms should also be considered. If empiric antibiotics are given, they should be discontinued when cultures and course warrant. A mortality rate of ≤5% is seen if 3 or fewer lobes are involved. Unless complications develop, such as infection or barotrauma, most patients recover in 2-3 wk. Prolonged lung damage may persist, including scarring, bronchiolitis obliterans, and bronchiectasis.

Prevention
Prevention of aspiration should always be the goal when airway manipulation is necessary for intubation or other invasive procedures. Feeding with enteral tubes passed beyond the pylorus, elevating the head of the bed 30-45 degrees in mechanically ventilated patients, and oral decontamination reduce the incidence of aspiration complications in the intensive care unit. Minimizing use of sedation, monitoring for gastric residuals, and gastric acid suppression may all help prevent aspiration. However, the latter is not without some controversy. Any patient with altered consciousness, especially one who is receiving tube feedings, should be considered at high risk for aspiration. Preoperative restriction of oral fluids to otherwise normal children for 6 hr does not appear to provide benefit compared to restriction for only 2 hr in terms of risk for aspiration.

HYDROCARBON ASPIRATION
Aspiration and resulting pneumonitis are typically the most dangerous consequences of acute hydrocarbon ingestion (see Chapter 63). Although significant pneumonitis occurs in <2% of all hydrocarbon ingestions, an estimated 20 deaths occur annually from hydrocarbon aspiration in both children and adults. Some of these deaths represent suicides. Hydrocarbons with lower surface tensions (gasoline,
turpentine, naphthalene) have more potential for aspiration toxicity than heavier mineral or fuel oils. Ingestion of >30 mL (approximate volume of an adult swallow) of hydrocarbon is associated with an increased risk of severe pneumonitis. Clinical findings including chest retractions, grunting, cough, and fever may occur as soon as 30 min after aspiration or may be delayed for several hours. Lung radiographic changes usually occur within 2-8 hr, peaking in 48-72 hr (Fig. 397-1). Pneumatoceles and pleural effusions may occur. Patients presenting with cough, shortness of breath, or hypoxemia are at high risk for pneumonitis. Persistent pulmonary function abnormalities can be present many years after hydrocarbon aspiration. Other organ systems, especially the liver, central nervous system, and heart, may suffer serious injury. Cardiac dysrhythmias may occur and may be exacerbated by hypoxia and acid–base or electrolyte disturbances.

**Treatment**

Gastric emptying is contraindicated in nearly all situations because the risk of aspiration is greater than any systemic toxicity. Treatment is generally supportive, consisting of oxygen, fluids, and ventilatory support, and rarely extracorporeal membrane oxygenation, as necessary. Exogenous surfactant administration has been described as helpful in case reports. The child who has no symptoms and normal chest radiograph findings should be observed for 6-8 hr to ensure safe discharge. Certain hydrocarbons have more inherent systemic toxicity. The pneumonic CHAMP refers collectively to the following hydrocarbons: camphor, halogenated carbons, aromatic hydrocarbons, and those associated with metals and pesticides. Patients who ingest these compounds in volumes >30 mL, such as might occur with intentional overdose, may benefit from gastric emptying. This is still a high-risk procedure that can result in further aspiration. If a cuffed endotracheal tube can be placed without inducing vomiting, this procedure should be considered, especially in the presence of altered mental status. Treatment of each case should be considered individually, with guidance from a poison control center.

Other substances that are particularly toxic and cause significant lung injury when aspirated or inhaled include baby powder, chlorine, shellac, beryllium, and mercury vapors. Repeated exposure to low concentrations of these agents can lead to chronic lung disease, such as interstitial pneumonitis and granuloma formation. Corticosteroids may help reduce fibrosis development and improve pulmonary function, although the evidence for this benefit is limited.

*Bibliography is available at Expert Consult.*
Bibliography
ETIOLOGY
Repeated aspiration of even small quantities of gastric, nasal, or oral contents can lead to recurrent bronchitis or bronchiolitis; recurrent pneumonia; atelectasis; wheezing; cough; apnea; and/or laryngospasm. Pathologic outcomes include granulomatous inflammation, interstitial inflammation, fibrosis, lipoid pneumonia, and bronchiolitis obliterans. Most cases clinically manifest as airway inflammation, and are rarely associated with significant morbidity. Table 398-1 lists underlying disorders that are frequently associated with recurrent aspiration. Oropharyngeal incoordination is reportedly the most common underlying problem associated with recurrent pneumonias in hospitalized children. In 2 reports, from 26-48% of such children were found to have dysphagia with aspiration as the underlying problem. Lipoid pneumonia may occur after the use of home/folk remedies involving oral or nasal administration of animal or vegetable oils to treat various childhood illnesses. Lipoid pneumonia has been reported as a complication of these practices in the Middle East, Asia, India, Brazil, and Mexico. The initial underlying disease, language barriers, and a belief that these are not “medications” may delay the diagnosis (see Chapter 4).

Gastroesophageal reflux disease (GERD; see Chapter 323) is also a common underlying finding that may predispose to recurrent respiratory disease, but it is less frequently associated with recurrent pneumonia than is dysphagia (see Chapter 323). GERD is associated with microaspiration and bronchiolitis obliterans in lung transplant recipients. Aspiration has also been observed in infants with respiratory symptoms but no other apparent abnormalities. Recurrent microaspiration has been reported in otherwise apparently normal newborns, especially premature infants. Aspiration is also a risk in patients suffering from acute respiratory illness from other causes, especially respiratory syncytial virus infection (see Chapter 260). Modified barium swallow and videofluoroscopy reveal silent aspiration in these patients. This finding emphasizes the need for a high degree of clinical suspicion for ongoing aspiration in a child with an acute respiratory illness, being fed enterally, who deteriorates unexpectedly.

DIAGNOSIS
Some underlying predisposing factors (see Table 398-1) are frequently clinically apparent but may require specific further evaluation. Initial
generally not indicated to establish a diagnosis of aspiration, may show infiltrates with decreased attenuation suggestive of lipoid pneumonia (Fig. 398-2). A carefully performed barium esophagram is useful in looking for anatomic abnormalities such as vascular ring, stricture, hiatal hernia, and tracheoesophageal fistula. It also yields qualitative information about esophageal motility and, when extended, of gastric emptying. However, primarily because of the very short viewing time, the esophagram is quite insensitive and nonspecific for aspiration or GERD. A modified barium swallow study with videofluoroscopy (videofluoroscopic swallowing study) is generally considered the gold standard for evaluating the swallowing mechanism. This study is preferably done with the assistance of a pediatric feeding specialist and a caregiver in the attempt to simulate the usual feeding technique of the child. The child is seated in normal eating position, and various consistencies of barium or barium-impregnated foods are offered. This study is more sensitive for demonstrating aspiration than bedside assessment or a traditional barium swallow study. The sensitivity of the modified barium swallow study is such that it occasionally detects aspiration in patients without apparent respiratory abnormalities.

The diagnosis begins with a detailed history and physical examination. The caregiver should be asked about spitting, vomiting, arching, or epigastric discomfort in an older child; the timing of symptoms in relation to feedings; positional changes; and nocturnal symptoms, such as coughing and wheezing. It is important to remember that coughing or gagging may be minimal or absent in a child with a depressed cough or gag reflex. Observation of a feeding is an essential part of the exam when a diagnosis of recurrent aspiration is being considered. Particular attention should be given to nasopharyngeal reflux, difficulty with sucking or swallowing, and associated coughing and choking. Voice changes (wet voice) and noisy (wet) breathing should be noted. The oral cavity should be inspected for gross abnormalities and stimulated to assess the gag reflex. Drooling or excessive accumulation of secretions in the mouth suggests dysphagia. Lung auscultation may reveal transient crackles or wheezes after feeding, particularly in the dependent lung segments.

The diagnosis of recurrent microaspiration is challenging because of the lack of highly specific and sensitive tests (Table 398-2). A plain chest radiograph is the usual initial study for a child in whom recurrent aspiration is suspected. The classic findings of segmental or lobar infiltrates localized to dependent areas may be found (Fig. 398-1), but there are a wide variety of radiographic findings. These findings include diffuse infiltrates, lobar infiltrates, bronchial wall thickening, hyperinflation, and even no detectable abnormalities. CT scans, though

### Table 398-1 Conditions Predisposing to Aspiration

<table>
<thead>
<tr>
<th>ANATOMICAL AND MECHANICAL</th>
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<tbody>
<tr>
<td>Tracheoesophageal fistula</td>
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<tr>
<td>Laryngeal cleft</td>
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<td>Vascular ring</td>
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<td>Cleft palate</td>
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<td>Micronascentia</td>
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<td>Macroglossia</td>
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<td>Achalasia</td>
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<td>Tracheostomy</td>
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<tr>
<td>Endotracheal tube</td>
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<td>Nasal or oral feeding tube</td>
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<tr>
<td>Collagen vascular disease (scleroderma, dermatomyositis)</td>
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<td>Gastroesophageal reflux disease</td>
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<td>Obesity</td>
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<tr>
<th>NEUROMUSCULAR</th>
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<tbody>
<tr>
<td>Altered consciousness</td>
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<td>Immaturity of swallowing/Prematurity</td>
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<td>Cerebral vascular accident</td>
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<tr>
<th>MISCELLANEOUS</th>
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<tr>
<td>Poor oral hygiene</td>
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<td>Prolonged hospitalization</td>
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<td>Gastric outlet or intestinal obstruction</td>
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<td>Poor feeding techniques (bottle propping, overfeeding, inappropriate foods for toddlers)</td>
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<tr>
<td>Bronchopulmonary dysplasia</td>
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<tr>
<td>Viral infection/bronchiolitis</td>
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</tbody>
</table>

**Figure 398-1** Chest radiograph of a developmentally delayed 15 yr old with chronic aspiration of oral formula. Note posterior (dependent areas) distribution with sparing of heart borders.

**Figure 398-2** Chest CT scan of same patient as in Figure 398-1. Note lung consolidation in dependent regions is of similar density to subcutaneous fat.
## Table 398-2  Summary of Diagnostic Tests of Aspiration

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>BENEFITS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiograph</td>
<td>Inexpensive and widely available Assesses accumulation of injury over time</td>
<td>Insensitive to early subtle changes of lung injury</td>
</tr>
<tr>
<td>High-resolution CT</td>
<td>Sensitive in detecting lung injury, such as bronchiectasis, tree-in-bud opacities, and bronchial thickening Less radiation than conventional CT Assesses accumulation of injury over time</td>
<td>More radiation exposure than plain radiograph</td>
</tr>
<tr>
<td>Video swallow study</td>
<td>Evaluates all phases of swallowing Evaluates multiple consistencies Feeding recommendations made at time of study</td>
<td>Information limited if child consumes only small quantities Difficult to perform in child who has not been feeding by mouth Radiation exposure proportional to study duration Cannot be performed at bedside Limited evaluation of anatomy Evaluates 1 moment in time</td>
</tr>
<tr>
<td>FEES/with sensory testing</td>
<td>Ability to thoroughly evaluate functional anatomy Evaluates multiple consistencies Can assess risk of aspiration in non-orally feeding child; airway protective reflexes can be assessed Feeding recommendations made at time of study Visual feedback for caregivers Can be performed at bedside No radiation exposure</td>
<td>Blind to esophageal phase and actual swallow Invasive and may not represent physiological swallowing conditions Evaluates 1 moment in time</td>
</tr>
<tr>
<td>BAL</td>
<td>Evaluates anatomy of entire upper and lower airways Samples the end-organ of damage Sample available for multiple cytological and microbiologic tests Widely available</td>
<td>Uncertainty regarding interpretation of lipid-laden macrophage index Index cumbersome to calculate Requires sedation or anesthesia Invasive Expensive</td>
</tr>
<tr>
<td>Esophageal pH monitoring</td>
<td>Current gold standard for diagnosis of Acid gastroesophageal reflux Established normative data in children</td>
<td>Blind to majority of reflux (nonacid) events Difficult to establish causal relationship between gastroesophageal reflux and aspiration Somewhat invasive Evaluates short time interval</td>
</tr>
<tr>
<td>Esophageal impedance</td>
<td>Likely gold standard for diagnosis of GERD with supraesophageal manifestations Able to detect acid and nonacid reflux events Detects proximal reflux events Able to evaluate for GERD without stopping medications</td>
<td>Lack of normative data for children Somewhat invasive Expensive and cumbersome to interpret Not widely available Evaluates short time interval</td>
</tr>
<tr>
<td>Gastroesophageal scintigraphy</td>
<td>Performed under physiologic conditions Low radiation exposure</td>
<td>Poor sensitivity May not differentiate between aspiration from dysphagia or GERD</td>
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<tr>
<td>Radionuclide salivagram</td>
<td>Child does not have to be challenged with food bolus Low radiation exposure</td>
<td>Unknown sensitivity Unknown relationship to disease outcomes Evaluates 1 moment in time</td>
</tr>
<tr>
<td>Dye studies</td>
<td>Can be constructed as screening test or confirmatory test Can evaluate aspiration of secretions or feeds Repeating over time allows for broader evaluation</td>
<td>Uncertainty in interpretation owing to variability of technique Can only be performed in children with tracheostomies</td>
</tr>
<tr>
<td>Other biomarkers (pepsin, bile acids) milk protein</td>
<td>Theoretical high specificity and sensitivity</td>
<td>Limited availability and standardization Variable results to date</td>
</tr>
</tbody>
</table>

BAL, bronchoalveolar lavage; FEES, fiberoptic-endoscopic evaluation of swallowing; GERD, gastroesophageal reflux disease.


A gastroesophageal “milk” scintiscan offers theoretical advantages over a barium swallow in being more physiologic and giving a longer window of viewing than the barium esophagram for detecting aspiration and GERD. However, this study has been found to have a low sensitivity and provides relatively little anatomic detail. Another radionuclide scan termed the “salivagram” may also be useful to assess aspiration of esophageal contents. When this scan is performed by experienced personnel, its sensitivity appears to be comparable to that of the modified barium swallow study. The use of fiberoptic endoscopic evaluation of swallowing has been found useful in adult and some pediatric patients, to observe swallowing directly without radiation exposure. The child’s reaction to placement of the endoscope may
alter the assessment of function, depending on level of comfort and cooperation.

Tracheobronchial aspirates can be examined for numerous entities to evaluate for aspiration. For patients with artificial airways, the use of an oral dye and visual examination of tracheal secretions is useful. This test should not be done on a chronic basis, such as in tube feedings, because of possible dye toxicity. In using this test acutely, the best method is to place a few drops of dye on the patient’s tongue and perform subsequent suctioning of the airway over the next several minutes. Quantitation of lipid-laden alveolar macrophages from bronchial aspirates has been shown to be a sensitive test for aspiration in children, but false-positive tests occur, especially with endobronchial obstruction, use of intravenous lipids, sepsis, and pulmonary bleeding. Bronchial washings may also be examined for various food substances, including lactose, glucose, food fibers, and milk antigens, as well as pepsin. Specificity and sensitivity of these tests have not been well studied.

**TREATMENT**

If chronic aspiration is associated with another underlying medical condition, treatment should be directed toward that problem. The level of morbidity from respiratory problems should determine the level of intervention. Often milder dysphagia can be treated with alteration of feeding position, limiting texture of foods to those best tolerated on modified barium esophagram (usually thicker foods), or limiting quantity per feeding. Currently evidence is lacking regarding the advisability of restricting oral intake of water by children whose aspiration is largely of thin fluids. Nasogastric tube feedings can be utilized temporarily during periods of transient vocal cord dysfunction or other dysphagia. Postpyloric feedings may also be helpful, especially if gastroesophageal reflux is present, although this does not eliminate reflux. There are several surgical procedures that may be considered. Tracheostomy (see Chapter 385.1), although sometimes predisposing to aspiration, may provide overall benefit from improved bronchial hygiene and the ability to suction aspirated material. Use of a one-way (Passy-Muir) valve on a tracheostomy tube has been shown to improve swallowing. Fundoplication with gastrostomy or jejunostomy feeding tube will reduce the probability of gastroesophageal reflux-induced aspiration, but recurrent pneumonias often persist because of dysphagia and presumed aspiration of upper airway secretions. Medical treatment with anticholinergics, such as glycopyrrolate or scopolamine, may significantly reduce morbidity from salivary aspiration but often has side effects. Aggressive surgical intervention with salivary gland excision, ductal ligation, laryngotracheal separation, or esophago gastric disconnection can be considered in severe, unresponsive cases. Although usually reserved for the most severe cases, surgical therapy may significantly improve quality of life and ease of care for some patients.

*Bibliography is available at Expert Consult.*
Bibliography
Immune and Inflammatory Lung Disease

Chapter 399

Hypersensitivity Pneumonia

Kevin J. Kelly

Hypersensitivity pneumonia (HP), aptly called extrinsic allergic alveolitis because the inciting agent is almost uniformly inhaled from the environment, is a complex immunologic-mediated syndrome of the pulmonary alveoli and interstitium. There are numerous specific disease names based on the origin of the offending antigen that is inhaled to describe HP. Prompt recognition of the signs and symptoms allows for complete reversal of the disease without long-term adverse consequences if the source of the exposure is recognized and abated. Failure to recognize the disease early may lead to chronic irreversible lung changes with persistent symptoms in the patient.

ETIOLOGY

The most common sources of offending agents that cause HP include agricultural aerosols, inhaled protein antigens from animals, antigens from microorganisms of bacteria, fungi, or protozoan origin, as well as chemicals of low and high molecular weight (Table 399-1). Although a large number of inciting agents are associated with occupational diseases in which children do not regularly work, there are many similar antigen sources in a nonoccupational environment and teenage work exposures that may occur causing the same disease. In addition to HP, the same antigens may lead to allergic asthma or chronic bronchitis as seen with animal proteins, contaminated metal working fluids, and other inhaled antigens.

Primary sources of HP in children have been the result of exposure to pet birds (or feathers in bedding) such as parakeets, canaries, cockatiels, or cockatoos or homes contaminated with pigeon antigens from home breeders or contamination. Humidifiers and hot tubs are notorious for contamination with thermophilic organisms as well as Mycobacterium avium complex. Mold from prior flooding or damp condensation represents an increasing problem experienced by clinicians since the building of homes with inadequate ventilation and insufficient air turnover. Allergic diseases such as asthma, chronic rhinitis, and HP may be seen from the same sources. Other family members may have symptoms of asthma or rhinitis while another may have HP.

CLASSIFICATION AND PATHOGENESIS

HP has been traditionally classified as acute, subacute, or chronic. This classification arose prior to more refined diagnostic modalities such as high-resolution computerized tomography (HRCT) scanning of the lungs and more refined immunologic diagnostic tests on bronchoalveolar lavage (BAL). Distinguishing chronic disease from subacute disease is difficult without clear differentiating criteria, but a diagnosis of HP at any stage results in the clinician recommending very specific interventions for improvement. HP is characterized as (1) acute nonprogressive and intermittent, (2) acute progressive and intermittent, (3) chronic nonprogressive, and (4) chronic progressive (Table 399-2).

The sensitivity of the complete criteria is lower than desired as not all patients will have abnormal radiography or the findings of positive precipitins to the offending antigen. The specificity of the criteria may also be problematic. Screening for pigeon breeder’s lung disease among a cohort of pigeon breeders will demonstrate that 30% or more of the pigeon breeders have immunoglobulin (Ig) G precipitins to pigeon dropping antigens while only a small number will have disease. Genetic and epigenetic factors yet to be identified are likely involved in determining who develops disease.

A diagnosis of HP is certain when the known exposure with immune response to the offending antigen is identified; the medical history and physical finding are abnormal on examination; BAL and lung biopsy are abnormal. Some clinicians have foregone the lung biopsy when a cluster of cases occurs and 1 patient biopsy is abnormal already. The immune mechanisms involved include morphologic changes seen with immune complex-mediated disease, especially in the acute phase, accompanied complement activation followed by delayed-type hypersensitivity response. The acute phase of the disease shows alveolitis with a mixed cellular infiltration with lymphocytes, macrophage, plasma cells, and neutrophils. Continued exposure results in the formation of loose, noncaseating granuloma located near the respiratory or terminal bronchioles. It is critical when a biopsy is being performed (transbronchial or surgical) that the pathologist knows that HP is being considered as there are other interstitial lung diseases that produce
<table>
<thead>
<tr>
<th>HYPERSENSITIVITY PNEUMONITIS</th>
<th>ANTIGEN SOURCE</th>
<th>HYPERSENSITIVITY PNEUMONITIS</th>
<th>ANTIGEN SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bagassosis (mold on pressed sugar cane)</strong></td>
<td>Thermoactinomyces sacchari Thermoactinomyces vulgaris</td>
<td><strong>Miller’s lung (dust-contaminated grain)</strong></td>
<td>Sitophilus granarius (i.e., wheat weevil)</td>
</tr>
<tr>
<td><strong>Bat lung (bat droppings)</strong></td>
<td>Bat serum protein</td>
<td><strong>Moldy hay, grain, silage (farmer’s lung)</strong></td>
<td>Thermophilic actinomycetes Fungi (e.g., Aspergillus umbrosus)</td>
</tr>
<tr>
<td><strong>Bible printer’s lung</strong></td>
<td>Moldy typesetting water</td>
<td><strong>Mollusk shell hypersensitivity pneumonitis</strong></td>
<td>Sea-snail shell</td>
</tr>
<tr>
<td><strong>Bird fancier’s lung (parakeets, budgerigars, pigeons)</strong></td>
<td>Droppings, feathers, serum proteins</td>
<td><strong>Mushroom worker’s lung</strong></td>
<td>Mushroom spores Thermophilic actinomycetes</td>
</tr>
<tr>
<td><strong>Byssinosis (“brown lung”) (unclear if a true cause of hypersensitivity pneumonitis; asthma is common)</strong></td>
<td>Cotton mill dust (carding and spinning areas of cotton, flax, and soft-hemp)</td>
<td><strong>Paprika slicer’s lung (moldy paprika pods)</strong></td>
<td>Mucor stolonifer</td>
</tr>
<tr>
<td><strong>Canary fancier’s lung</strong></td>
<td>Serum proteins</td>
<td><strong>Pauli’s reagent alveolitis</strong></td>
<td>Sodium diazobenzene sulfate</td>
</tr>
<tr>
<td><strong>Cheese washer’s lung (moldy cheese)</strong></td>
<td>Penicillium casei Aspergillus clavatus</td>
<td><strong>Pearl oyster shell pneumonitis</strong></td>
<td>Oyster shells</td>
</tr>
<tr>
<td><strong>Chemical hypersensitivity pneumonitis</strong></td>
<td>Diphenylmethane diisocyanate (MDI) Toluene diisocyanate (TDI)</td>
<td><strong>Pituitary snuff taker’s disease</strong></td>
<td>Dried, powdered cattle or pig pituitary proteins</td>
</tr>
<tr>
<td><strong>Coffee worker’s lung</strong></td>
<td>Coffee-bean dust</td>
<td><strong>Potato riddler’s lung (moldy hay around potatoes)</strong></td>
<td>Thermophilic actinomycetes T. vulgaris Faenia rectivirgula Aspergillus spp.</td>
</tr>
<tr>
<td><strong>Composter’s lung</strong></td>
<td>T. vulgaris Aspergillus species</td>
<td><strong>Poultry worker’s lung (feather plucker’s disease)</strong></td>
<td>Serum proteins (chicken products)</td>
</tr>
<tr>
<td><strong>Contaminated basement (sewage) pneumonitis</strong></td>
<td>Cephalosporium</td>
<td><strong>Pyrethrum (pesticide)</strong></td>
<td>Pyrethrum</td>
</tr>
<tr>
<td><strong>Coptic lung (mummy handler’s lung)</strong></td>
<td>Cloth wrappings of mummies</td>
<td><strong>Sauna taker’s lung</strong></td>
<td>Aureobasidium spp., other sources</td>
</tr>
<tr>
<td><strong>Detergent worker’s lung (washing powder lung)</strong></td>
<td>Bacillus subtilis enzymes</td>
<td><strong>Sequiosis (moldy wood dust)</strong></td>
<td>Graphium Pullularia Trichoderma spp. Aureobasidium pullulans</td>
</tr>
<tr>
<td><strong>Dry rot lung</strong></td>
<td>M penilus lacrymans</td>
<td><strong>Suberosis (moldy cork dust)</strong></td>
<td>Thermactinomyces viridis Penicillium glabrum Aspergillus conidia</td>
</tr>
<tr>
<td><strong>Duck fever</strong></td>
<td>Feathers, serum proteins</td>
<td><strong>Summer-type pneumonitis</strong></td>
<td>Trichosporon cutaneum</td>
</tr>
<tr>
<td><strong>Epoxy resin lung</strong></td>
<td>Phthalic anhydride (heated epoxy resin)</td>
<td><strong>Tea grower’s lung</strong></td>
<td>Tea plants</td>
</tr>
<tr>
<td><strong>Esparto dust (mold in plaster dust)</strong></td>
<td>Aspergillus fumigatus Thermophilic actinomycetes</td>
<td><strong>Thatched-roof lung (huts in New Guinea)</strong></td>
<td>Saccharomonspora viridis (dead grasses and leaves)</td>
</tr>
<tr>
<td><strong>Fish meal worker’s lung</strong></td>
<td>Fish meal</td>
<td><strong>Turkey handling disease</strong></td>
<td>Serum proteins (turkey products)</td>
</tr>
<tr>
<td><strong>Furrier’s lung (sewing furs; animal fur dust)</strong></td>
<td>Animal pelts</td>
<td><strong>Unventilated shower</strong></td>
<td>Epicoccum nigrum</td>
</tr>
<tr>
<td><strong>Grain measurer’s lung</strong></td>
<td>Cereal grain (Sporobolomyces) Grain dust (mixture of dust, silica, fungi, insects, and mites)</td>
<td><strong>Upholstery fabric (nylon filament, cotton/polyester, and latex adhesive)</strong></td>
<td>Aflatoxin-producing fungus, Fusarium spp.</td>
</tr>
<tr>
<td><strong>Hot-tub lung (mists; mold on ceiling and around tub)</strong></td>
<td>Cladosporium spp. Mycobacterium avium complex</td>
<td><strong>Velvet worker’s lung</strong></td>
<td>Unknown (? nylon velvet fiber, tannic acid, potato starch)</td>
</tr>
<tr>
<td><strong>Humidifier fever</strong></td>
<td>Thermoactinomyces (T. vulgaris, T. sacchari, T. candidus) Klebsiella oxytoca Naegleria gruberi Acanthamoeba polyphaga Acanthamoeba castellani</td>
<td><strong>Vineyard sprayer’s lung</strong></td>
<td>Copper sulfate (bordeaux mixture)</td>
</tr>
<tr>
<td><strong>Laboratory worker’s lung (rats, gerbils)</strong></td>
<td>Urine, serum, pelts, proteins</td>
<td><strong>Wine maker’s lung (mold on grapes)</strong></td>
<td>Botrytis cinerea</td>
</tr>
<tr>
<td><strong>Lifeguard lung</strong></td>
<td>Aerosolized endotoxin from pool-water sprays and fountains</td>
<td><strong>Wood dust pneumonitis (oak, cedar, and mahogany dust, pine and spruce pulp)</strong></td>
<td>Alternaria spp. Bacillus subtilis</td>
</tr>
<tr>
<td><strong>Lycopodanosis (Lycopodan puffballs)</strong></td>
<td>Puffball spores</td>
<td><strong>Wood pulp worker’s disease (oak and maple trees)</strong></td>
<td>Penicillium spp.</td>
</tr>
<tr>
<td><strong>Machine operator’s lung</strong></td>
<td>Pseudomonas fluorescens Aerosolized metal working fluid</td>
<td><strong>Wood trimmer’s disease (contaminated wood trimmings)</strong></td>
<td>Rhizopus spp., Mucor spp.</td>
</tr>
<tr>
<td><strong>Malt worker’s disease (moldy barley)</strong></td>
<td>Aspergillus fumigatus, Aspergillus clavatus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maple bark disease (moldy maple bark)</strong></td>
<td>Cryptostroma corticale</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
similar granulomas with subtle location differences depending on their origin.

**CLINICAL MANIFESTATIONS**

Heavy exposure to an offending antigen may lead to **acute HP**. This is the most common form of exposure but is still frequently not recognized. Symptoms are confused with bacterial or viral disease leading to treatment with antibiotics. Four to 6 hr after exposure the abrupt onset of cough, chest tightness, dyspnea, fever, chills, and fatigue are common (Table 399-3). Rarely, findings of wheezing are present on the initial examination. Rather, tachypnea with fine crackles may be heard by auscultation in the lung bases. However, auscultation may be normal to treatment with antibiotics. Four to 6 hr after antigen exposure.

**LABORATORY**

Most of the abnormal laboratory findings in hypersensitivity pneumonitis are not specific and represent evidence of activated inflammatory markers or lung injury. Nonspecific elevation of immune globulins or the erythrocyte sedimentation rate and C-reactive protein may also be found. Circulating immune complexes may be detected. Lactate dehydrogenase may be elevated in the presence of lung inflammation and normalizes with response to therapy.

Serum IgG precipitins to the offending agent are frequently positive given some caveats. Commercial antigen sources from animals and birds may contain insufficient antigen for precipitation. Some laboratories performing these tests on an infrequent basis often have false-negative tests presumed to be a result of commercial antigens lacking the proper epitopes for precipitation. It is critical that laboratories familiar with the performance of these tests be utilized. Those laboratories often recognize the value of processing antigens for precipitation from the environmental source directly as the test substrate with patient serum. Skin testing for IgE-mediated disease is not warranted unless there is evidence of mixed lung pathology such as asthma and interstitial lung opacities.

**Lung Biopsy**

Lung biopsy is necessary to confirm a diagnosis of HP. This is in sharp contrast to other lymphocytic granulomatous disease, like sarcoidosis, where the CD4:CD8 is ≥2, or pulmonary fibrosis associated with connective tissue disease. Cryptogenic organizing pneumonia, a rare disease in children, also may present with HP, the most common form of exposure but is still frequently not recognized. Symptoms are confused with bacterial or viral disease leading to treatment with antibiotics. Four to 6 hr after exposure the abrupt onset of cough, chest tightness, dyspnea, fever, chills, and fatigue are common (Table 399-3). Rarely, findings of wheezing are present on the initial examination. Rather, tachypnea with fine crackles may be heard by auscultation in the lung bases. However, auscultation may be normal at this stage. When **recurrent subacute disease** is present, the symptoms become progressive with weight loss, loss of appetite, and productive cough. When HP becomes **chronic** and progressive, the patient’s fingers become clubbed accompanied by persistent symptoms noted above denoting a deteriorating status. If the disease progresses to interstitial fibrosis, the symptoms tend to not respond to therapy and denote a state where mortality risk is increased. Histology is hard to distinguish from **idiopathic pulmonary fibrosis** at this stage.

**Table 399-2** Criteria Used in the Diagnosis of Hypersensitivity Pneumonitis

1. Identified exposure to offending antigen(s) by:
   - Medical history of exposure to suspected antigen in the patient’s living environment
   - Investigations of the environment confirm the presence of an inactivating antigen
   - Identification of specific immune responses (immunoglobulin G serum precipitin antibodies against the identified antigen) are suggestive of the potential etiology but are insufficient in isolation to confirm a diagnosis
2. Clinical, radiographic, or physiologic findings compatible with hypersensitivity pneumonitis:
   - Respiratory and often constitutional signs and symptoms
   - Crackles on auscultation of the chest
   - Weight loss
   - Cough
   - Breathlessness
   - Episodic fever
   - Wheezing
   - Fatigue

**NOTE:** These findings are especially suggestive of hypersensitivity pneumonitis when they appear or worsen several hours after antigen exposure.

- A reticular, nodular, or ground glass opacities on chest radiograph or high-resolution CT
- Abnormalities in the following pulmonary function tests
  - Spirometry (restrictive, obstructive, or mixed patterns)
  - Lung volumes (low or high)
  - Reduced diffusion capacity by carbon monoxide
  - Altered gas exchange either at rest or with exercise (reduced partial pressure of arterial oxygen by blood gas or pulse oximeter testing)

**Table 399-3** Clinical History Clues Leading to a Diagnosis of Hypersensitivity Pneumonitis

- Recurrent pneumonia
- Pneumonia after repeat exposures (week, season, situation)
- Cough, fever, and chest symptoms after making a job change or home change
- Cough, fever, wheezing after return to school or only at school
- Pet exposure (especially birds that shed dust such as pigeons, canaries, cockatiels, cockatoos)
- Bird contaminant exposure (e.g., pigeon infestation)
- Farm exposure to birds and hay
- History of water damage despite typical cleaning
- Use of hot tub, sauna, swimming pool
- Other family members or workers with similar recurrent symptoms
- Improvement after temporary environment change (e.g., vacation)

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pathologist about the suspicion of HP so that the findings can be interpreted appropriately.

Poorly formed, noncaseating granulomas are seen near the respiratory and terminal bronchioles on histology with multinucleated giant cells. This is in sharp contrast to the granuloma of sarcoidosis that are well formed. Lymphocytes and plasma cells infiltrate the alveolar walls predominantly in a bronchocentric pattern. Fibrosis in the peribronchioriole region supports a diagnosis of HP. Foamy cytoplasm accompanying large histiocytes in the alveoli and interstitium may be characteristically found.

**Radiology**

Chest radiograph almost always precedes the use of HRCT of the chest in children because of the need for sedation and concerns regarding risk of irradiation dose from HRCT. The plain radiograph will often demonstrate a ground-glass appearance, interstitial prominence, with a predominant location in the upper and middle lung fields. It is common for a chest radiograph to be considered normal by a radiologist early in the disease progression. Late in the disease, interstitial fibrosis may become prominent in the presence of increasing dyspnea, hypoxemia on room air, and even clubbing of the fingers. Mediastinum widening from lymphadenopathy is not usually present; when present, the lymph nodes are prominent along the airway near the carina, suggesting that the antigen source is inhaled and being responded to by the immune system.

Classical findings of mid zone and upper zone opacities with ground-glass appearance and nodularity on HRCT in the presence of typical clinical exam HP findings (lung crackles, cough, dyspnea) and lymphocytosis on BAL are almost sufficient to make a diagnosis (Fig. 399-1). These finding must prompt the clinician to identify the exposure in order to secure the diagnosis and eliminate the offending antigen. Without therapy, the progressive inflammatory response leads to air trapping, honeycombing, emphysema, and mild fibrosis in the chronic state. It is in this latter stage that idiopathic pulmonary fibrosis and nonspecific interstitial fibrosis are hard to differentiate. Whether true idiopathic pulmonary fibrosis exists in children with fibroblast foci are found on biopsy with usual interstitial fibrosis has been questioned.

**Antigen Challenge By Inhalation**

Inhalation challenge can be performed by 2 methods: (1) reexposure of the patient to the environment where the suspected antigen is present and (2) direct inhalation challenge at the hospital to material collected from the suspected source of the antigen. As the second method has resulted in severe exacerbation of disease in some individuals, its use is discouraged (see Chapter 399.2).

Two abnormal responses may be seen. Most commonly, where there is HP without asthma, symptoms occur 6-12 hr after direct challenge in the hospital or reexposure at source of the antigen. The challenges replicate some or all of the symptoms observed in the presenting syndrome with fever, dyspnea, fatigue, and crackles on lung auscultation. Blood drawn prior to challenge and then repeated during these symptoms often demonstrate an increased neutrophil count compared to baseline. Pulmonary function tests demonstrate a fall in forced vital capacity and often a concurrent fall in the forced expiratory volume at 1 sec (FEV₁) with a stable or increasing ratio of FEV₁/forced vital capacity percentage. Hypoxemia may accompany this decline in pulmonary function as well as a fall in the diffusion capacity of carbon monoxide (DLCO). To see the complete effect, exercise during this period may show a considerable fall in oxygenation despite normal arterial blood gas oxygen tension and normal pulse oximetry at rest. This finding denotes the onset of worsening restrictive lung disease. Some patients may also demonstrate an early and late reduction in the FEV₁ as is seen in allergen challenge with asthma. In this dual reaction, the forced vital capacity also declines and is often accompanied by fever and leukocytosis.

**TREATMENT**

The control of environmental exposure to the offending antigen is a key to curing HP and remains the ideal method of treatment and prevention of recurrence. Counseling about the risk to children of exposure to birds and feathered bedding, or other environmental antigens, biologic aerosols, or agriculture dusts that are known to induce HP are important. Certainly, the source of the antigen and type of antigen appears to affect response to treatment and long-term prognosis. Older individuals who contract farmer's lung are likely to recover with minimal permanent residual effect, whereas individuals with bird fancier's lungs from antigens produced by pigeons have a worse prognosis, especially if fibrosis is detected on lung biopsy. The pediatrician should advise—in the strongest terms—removal of the antigen source from the affected child's environment. This may be an extraordinary challenge given various children's living circumstances and lack of independent control of the environment they live in.

In addition, pediatricians should be familiar with recommendations about the maintenance of heating, ventilation, and air conditioning systems, as well as of humidifiers and vaporizers. Daily drainage, cleansing of residue, and routine cleaning with hydrogen peroxide or bleach help to rid humidifiers and vaporizers of harmful pathogens that cause HP.

Glucocorticosteroids at a dose of 0.5-1 mg/kg/day of prednisone or equivalent will reduce the immune inflammatory response in the
lungs. Comparative trials in adults demonstrate that the use of 4 wks of therapy is as effective as 12 wks of therapy. Removal of antigen alone is sufficient to normalize lung function in most patients, but symptoms and pulmonary functions return to normal faster with the use of glucocorticoids. Because of the rapid reversal of symptoms, successful abatement of the environment is sometimes compromised when the family sees improvement prior to the antigen source removal.

Bibliography is available at Expert Consult.

399.2 Occupational and Environmental Lung Disease
Kevin J. Kelly

Occupational and environmental lung diseases constitute a larger part of primary care pediatrics, pediatric emergency medicine, and other pediatric subspecialties than most pediatric practitioners expect or realize. Although occupational and environmental lung diseases includes occupational asthma, reactive airways dysfunction syndrome (RADS), HP, hard metal inhalation lung disease, berylliosis, and air pollution, this chapter focuses on occupational asthma and RADS. Berylliosis has a propensity to form granulomas (see Chapter 399.3). Although some diseases will be seen with regularity, the important role that a part-time workplace, school, daycare, neighbors’ housing, multiple family housing, and indoor and outdoor environments may have in the causation of signs and symptoms in the patient is not always considered by the clinician.

The vast array of exposures shown to cause disease of the lungs is daunting, such as the inhalation of baking flour or household cleaning fluids causing asthma, microwave popcorn exposure to diacetyl resulting in bronchiolitis obliterans, and exposure to thermophilic organisms or mold resulting in hypersensitivity pneumonitis. The acute eosinophilic pneumonias associated with new onset of smoking and chemical inhalation of 1,1,1-trichloroethane (Scotchgard) require a high index of suspicion and unique lines of questioning. The same antigen encountered in a work, school, home, or outdoor environment may result in different disease presentation because of host factors, dose exposure, and genetic susceptibility. One of the most prominent examples is an investigation of workers who inhaled metal working fluid resulting in the development of asthma, HP, chronic bronchitis, or no symptoms at all from similar exposures. Immunologic evaluation in some exposures has shown similar immune responses in different individuals, but a wide range of disease provocation. When high molecular weight proteins cause asthma, symptoms of rhinoconjunctivitis frequently precede the onset of pulmonary symptoms. The medical history in occupational and environmental lung diseases has used an expanded construct with a simple acronym, WHACOS (Table 399-4).

It is important to remember that in patients with occupational- or environmental-induced disease, the onset of symptoms has a lag time between exposure and symptoms. In occupational asthma, there may be an immediate response within 1-2 hr of exposure, demonstrated as a decline in pulmonary function, specifically the FEV1. Usually, lung function returns to normal spontaneously unless persistent exposure occurs. Some patients demonstrate no immediate reduction in lung function, but rather experience a delayed response of 4-6 hr after the exposure. Treating physicians can take advantage of this physiology in occupational and environmental asthma by use of spirometry before and after work or school peak flow measurements hourly during exposure and after leaving the exposure. Because workers and children in school have prolonged periods of exposure followed by a number of days without exposure, the use of pulmonary function plus bronchial hyperresponsiveness testing is helpful. Pulmonary function tests prior to starting work on a Monday of a typical work week may be normal. By Friday of a typical work or school week, the baseline pulmonary functions may have fallen and bronchial responsiveness may have become more sensitive to a lower concentration of histamine, methacholine, or mannitol. By Monday, the tests may have returned to normal or near normal with no change other than reduced exposure.

In the case of HP, a lag of 4-8 hr between the time of exposure and onset of fever, cough, and dyspnea is common. Unfortunately, the return home from hospitalization for culture-negative pneumonia to a source of antigen causing HP often results in complete reocurrence of symptoms. Clinicians must have a high index of suspicion for HP with reocurrence of pulmonary infiltrates shortly after reexposure (see Chapter 399.1).

CLASSIFICATION AND PATHOGENESIS
Occupational and environmental lung diseases include numerous syndromes of human lung disease such as occupational asthma, RADS, reactive upper airway disease syndrome, hypersensitivity pneumonitis (see Chapter 399.1), air pollution–induced disease, hard metal inhalation lung disease, berylliosis, occupation-induced lung cancer (e.g., mesothelioma from asbestosis), and chronic obstructive pulmonary disease without smoking. Most of these diseases are not problematic for children but adolescents may be exposed through part-time work or by single exposures as seen in RADS.

Occupational and Environmental Asthma
The general principles of diagnosis, clinical signs and symptoms, treatment, and causes of asthma are discussed in Chapter 144. High molecular weight causes of occupational and environmental asthma can be characterized as allergens, which are normally proteins and enzymes, inhaled from multiple sources (Table 399-5). These include various animals, shellfish, fish, enzymes (e.g., Bacillus subtilis in laundry detergent), and flour or cereals. Occupational and environmental asthma is also caused by a number of low molecular weight chemicals (Table 399-6). These chemicals are sufficient to induce an immune response but it is often not by an IgE-mediated mechanism. These chemicals appear to act as haptons that bind to human proteins, causing an immune response in the human host.

The pathogenesis of asthma in patients exposed to high molecular weight antigens follows the experience of nonoccupational asthma in patients where atopy, gender, genetics, concentration of antigen, duration of exposure, and other individual factors all contribute to the development of disease. Most individuals require a concentration and duration of exposure sufficient to cause IgE antibody sensitization to the offending allergen with development of bronchial hyperresponsiveness and airway inflammatory disease. If the allergen exposure is sufficient, these proteins can drive the immune response to a T-lymphocyte type 2 phenotype, even in patients without prior atopic disposition, as occurred in the case of latex allergy where many nonatopic individuals and patients exposed to allergen in their personal healthcare developed occupational allergy to multiple proteins from natural rubber latex. Atopic individuals are at the highest risk of developing latex allergy. A longitudinal study demonstrated that powdered latex gloves with high allergen content were the reason for the epidemic of latex allergy and
Bibliography
### Table 399-5: High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma

<table>
<thead>
<tr>
<th>OCCUPATION OR ENVIRONMENT</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANIMAL-DERIVED ANTIGENS</strong></td>
<td></td>
</tr>
<tr>
<td>Agricultural worker</td>
<td>Cow dander</td>
</tr>
<tr>
<td>Baker</td>
<td>Lactalbumin</td>
</tr>
<tr>
<td>Butcher</td>
<td>Cow bone dust, pig, goat dander</td>
</tr>
<tr>
<td>Dairy industry</td>
<td>Raw beef</td>
</tr>
<tr>
<td>Egg producer</td>
<td>Egg protein</td>
</tr>
<tr>
<td>Farmer</td>
<td>Deer dander, mink urine</td>
</tr>
<tr>
<td>Frog catcher</td>
<td>Frog</td>
</tr>
<tr>
<td>Hairdresser</td>
<td>Sericin</td>
</tr>
<tr>
<td>Ivory worker</td>
<td>Ivory dust</td>
</tr>
<tr>
<td>Laboratory technician</td>
<td>Bovine serum albumin, laboratory animal, monkey dander</td>
</tr>
<tr>
<td>Nacre buttons</td>
<td>Nacre dust</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>Endocrine glands</td>
</tr>
<tr>
<td>Pork producer</td>
<td>Pig gut (vapor from soaking water)</td>
</tr>
<tr>
<td>Poultry worker</td>
<td>Chicken</td>
</tr>
<tr>
<td>Tanner</td>
<td>Casein (cow’s milk)</td>
</tr>
<tr>
<td>Various</td>
<td>Bat guano</td>
</tr>
<tr>
<td>Veterinarian</td>
<td>Goat dander</td>
</tr>
<tr>
<td>Zookeeper</td>
<td>Birds</td>
</tr>
<tr>
<td><strong>CRUSTACEANS, SEAFOOD, FISH</strong></td>
<td></td>
</tr>
<tr>
<td>Canning factory</td>
<td>Octopus</td>
</tr>
<tr>
<td>Diet product</td>
<td>Shark cartilage</td>
</tr>
<tr>
<td>Fish food factory</td>
<td>Gammarus shrimp</td>
</tr>
<tr>
<td>Fish processor</td>
<td>Clam, shrimp, crab, prawn, salmon, trout, lobster, turbot, various fishes</td>
</tr>
<tr>
<td>Fisherman</td>
<td>Red soft coral, cuttlefish</td>
</tr>
<tr>
<td>Jewelry polisher</td>
<td>Cuttlefish bone</td>
</tr>
<tr>
<td>Laboratory grinder</td>
<td>Marine sponge</td>
</tr>
<tr>
<td>Oyster farm</td>
<td>Hoya (oyster farm prawn or sea-squirt)</td>
</tr>
<tr>
<td>Restaurant seafood handler</td>
<td>Scallops and shrimp</td>
</tr>
<tr>
<td>Scallop plant processor</td>
<td>King scallop and queen scallop</td>
</tr>
<tr>
<td>Technician</td>
<td>Shrimp meal (Artemia salina)</td>
</tr>
<tr>
<td><strong>ARTHROPODS</strong></td>
<td></td>
</tr>
<tr>
<td>Agronomist</td>
<td>Bruchus lentis</td>
</tr>
<tr>
<td>Bottling</td>
<td>Ground bug</td>
</tr>
<tr>
<td>Chicken breeder</td>
<td>Herring worm (Anisakis simplex)</td>
</tr>
<tr>
<td>Engineer at electric power plant</td>
<td>Caddis flies (Ptyryganeidae)</td>
</tr>
<tr>
<td>Entomologist</td>
<td>Lesser mealworm (Alphitobius diapeninus Panzer), moth, butterfly</td>
</tr>
<tr>
<td>Farmer</td>
<td>Grain pests (Eurygaster and Pyrale)</td>
</tr>
<tr>
<td>Fish bait handler</td>
<td>Insect larvae (Galleria mellonella), mealworm larvae (Tenebrio molitor), green bottle fly larvae (Lucila caesar), daphnia, fish-feed Echinodorus larva (Echinodorus plasmosus), Chiromids midge (Chironomus thumili thumili)</td>
</tr>
<tr>
<td>Fish processing</td>
<td>Herring worm (Anisakis simplex)</td>
</tr>
<tr>
<td>Flight crew</td>
<td>Screw worm fly (Cochliomyia hominivorax)</td>
</tr>
<tr>
<td>Honey processors</td>
<td>Honeybee</td>
</tr>
<tr>
<td>Laboratory worker</td>
<td>Cricket, fruit fly, grasshopper (Locusta migratoria), locust</td>
</tr>
<tr>
<td>Mechanic in a rye plant</td>
<td>Confused flour beetle (Tricholoma confusum)</td>
</tr>
<tr>
<td>Museum curator</td>
<td>Beetles (Coleoptera)</td>
</tr>
<tr>
<td>Seed house</td>
<td>Mexican bean weevil (Zabrotes subfasciatus)</td>
</tr>
<tr>
<td>Sericulture</td>
<td>Silkworm, larva of silkworm</td>
</tr>
<tr>
<td>Sewage plant worker</td>
<td>Sewer fly (Psychoda alternata)</td>
</tr>
<tr>
<td>Technician</td>
<td>Arthropods (Chrysopelea carnea, Leptinotarsa decemlineata, Ostrinia nubilalis, and Ephesia kuehniella), sheep blowfly (Lucilia cuprina)</td>
</tr>
<tr>
<td>Wool worker</td>
<td>Dermestidae spp.</td>
</tr>
<tr>
<td><strong>ACARIANS</strong></td>
<td></td>
</tr>
<tr>
<td>Apple grower</td>
<td>Fruit tree red spider mite (Panonychus ulmi)</td>
</tr>
<tr>
<td>Citrus farmer</td>
<td>Citrus red mite (Panonychus citri)</td>
</tr>
<tr>
<td>Farmer</td>
<td>Barn mite, two-spotted spider mite (Tetranychus urticae), grain mite</td>
</tr>
<tr>
<td>Flour handler</td>
<td>Mites and parasites</td>
</tr>
<tr>
<td>Grain-store worker</td>
<td>Grain mite</td>
</tr>
<tr>
<td>Horticulturist</td>
<td>Amblyseius cucumeris</td>
</tr>
<tr>
<td>Poultry worker</td>
<td>Fowl mite</td>
</tr>
<tr>
<td>Vine grower</td>
<td>McDaniel spider mite (Tetranychus mcdanielli)</td>
</tr>
<tr>
<td><strong>MOLDS</strong></td>
<td></td>
</tr>
<tr>
<td>Agriculture</td>
<td>Plasmodora viticola</td>
</tr>
<tr>
<td>Baker</td>
<td>Alternaria, Aspergillus (unspecified)</td>
</tr>
<tr>
<td>Beet sugar worker</td>
<td>Aspergillus (unspecified)</td>
</tr>
<tr>
<td>Coal miner</td>
<td>Rhizopus nigricans</td>
</tr>
<tr>
<td>Coffee maker</td>
<td>Chrysosonia stiptafoxia</td>
</tr>
<tr>
<td>Laborer</td>
<td>Sooty molds (Ascomycetes, deuteromycetes)</td>
</tr>
<tr>
<td>Logging worker</td>
<td>Chrysosonia stiptafoxia</td>
</tr>
<tr>
<td>Plywood factory worker</td>
<td>Neurospora</td>
</tr>
<tr>
<td>Sausage processing</td>
<td>Penicillium nalgiovense</td>
</tr>
<tr>
<td>Sawmill worker</td>
<td>Trichoderma koningii</td>
</tr>
<tr>
<td>Stucco worker</td>
<td>Mucor spp. (contaminating esparto fibers)</td>
</tr>
<tr>
<td>Technician</td>
<td>Dicyostelium discoideum (mold), Aspergillus niger</td>
</tr>
<tr>
<td><strong>MUSHROOMS</strong></td>
<td></td>
</tr>
<tr>
<td>Agriculture</td>
<td>Agaricus bisporus (white mushroom)</td>
</tr>
<tr>
<td>Baker</td>
<td>Baker’s yeast (Saccharomyces cerevisiae), Boletus edulis</td>
</tr>
<tr>
<td>Greenhouse worker</td>
<td>Sweet pea (Lathyrus odoratus)</td>
</tr>
<tr>
<td>Hotel manager</td>
<td>Boletus edulis</td>
</tr>
<tr>
<td>Mushroom producer</td>
<td>Pleurotus comocopae</td>
</tr>
<tr>
<td>Mushroom soup processor</td>
<td>Mushroom unspecified</td>
</tr>
<tr>
<td>Office worker</td>
<td>Boletus edulis</td>
</tr>
<tr>
<td>Seller</td>
<td>Pleurotus ostreatus (spores of white spongy rot)</td>
</tr>
<tr>
<td><strong>ALGAE</strong></td>
<td></td>
</tr>
<tr>
<td>Pharmacist</td>
<td>Chlorella</td>
</tr>
<tr>
<td>Thalassotherapist</td>
<td>Algae (species unspecified)</td>
</tr>
<tr>
<td><strong>FLOURS</strong></td>
<td></td>
</tr>
<tr>
<td>Animal fodder</td>
<td>Marigold flour (Tagetes erecta)</td>
</tr>
<tr>
<td>Baker</td>
<td>Wheat, rye, soya, and buckwheat flour; Konjac flour; white pea flour (Lathyrus sativus)</td>
</tr>
<tr>
<td><strong>POLENS</strong></td>
<td></td>
</tr>
<tr>
<td>Florist</td>
<td>Cyclamen, rose</td>
</tr>
<tr>
<td>Gardener</td>
<td>Canary island date palm (Phoenix canariensis), Bell of Ireland (Moluccella laevis), Bell pepper, chrysanthemum, eggplant (Solanum melongena), Brassica oleracea (cauliflower and broccoli)</td>
</tr>
<tr>
<td>Laboratory worker</td>
<td>Sunflower (Helianthus spp.), thale cress (Arabidopsis thaliana)</td>
</tr>
<tr>
<td>Olive farmers</td>
<td>White mustard (Sinapis alba)</td>
</tr>
<tr>
<td>Processing worker</td>
<td>Helianthus annuus</td>
</tr>
</tbody>
</table>
### Table 399-5  High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma—cont’d

<table>
<thead>
<tr>
<th>OCCUPATION OR ENVIRONMENT</th>
<th>SOURCE</th>
<th>OCCUPATION OR ENVIRONMENT</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PLANTS</strong></td>
<td></td>
<td><strong>BIOLOGIC ENZYMES</strong></td>
<td></td>
</tr>
<tr>
<td>Brewery chemist</td>
<td>Hops</td>
<td>Baker</td>
<td>Fiction amylose, fungal amyloglucosidase and hemicellulase</td>
</tr>
<tr>
<td>Brush-makers</td>
<td>Tampico fiber in agave leaves</td>
<td>Detergent industry</td>
<td>Various enzymes in rennet production (proteases, pepsine, chymosines)</td>
</tr>
<tr>
<td>Butcher</td>
<td>Aromatic herb</td>
<td>Factory worker</td>
<td>Esterase, Bacillus subtilis</td>
</tr>
<tr>
<td>Chemist</td>
<td>Linseed oilcake, Voacanga africana seed dust</td>
<td>Hospital personnel</td>
<td>Bacillus subtilis</td>
</tr>
<tr>
<td>Cosmetics</td>
<td>Dusts from seeds of Sacha Inchi (Plukenetia volubilis), chamomile (unspecified)</td>
<td>Laboratory worker</td>
<td>Pectinase and glucanase</td>
</tr>
<tr>
<td>Decorator</td>
<td>Cocoon seed (Entage gigas)</td>
<td>Pharmaceutical</td>
<td>Empyrase (pronase B)</td>
</tr>
<tr>
<td>Floral worker</td>
<td>Decorative flower, safflower (Carthamus tinctorius) and yarrow (Achillea millefolium), spathe flower, statues (Limonium tataricum), baby’s breath (Gypsophila paniculata), ivy (Hedera helix), flower (various), sea lavender (Limonium sinatum)</td>
<td>Tobacco manufacturer</td>
<td>Xylanase, phytase from</td>
</tr>
<tr>
<td>Food industry</td>
<td>Aniseed, fenugreek, peach, garlic dust, asparagus, coffee bean, sesame seed, grain dust, carrot (Daucus carota L.), green bean (Phaseolus multiformis), lime bean (Phaseolus lunatus), onion, potato, swiss chard (Beta vulgaris L.), courgette, carob bean, spinach powder, cauliflower, cabbage, chicory, fennel seed, onion seeds (Allium cepa, red onion), rice, saffron (Crocus sativus), spices, grain dust</td>
<td>Tobacco leaf</td>
<td>Trypsin</td>
</tr>
<tr>
<td>Gardener</td>
<td>Copperleaf (Acalypha wilkesiana), grass juice, weeping fig (Ficus benjamina), umbrella tree (Schefflera spp.), amaryllis (Hippeastrum spp.), Madagascar jasmine sap (Stephanotis floribunda), vetch (Vicia sativa)</td>
<td>Decorator</td>
<td>Plastic</td>
</tr>
<tr>
<td>Hairdresser</td>
<td>Henna (unspecified)</td>
<td>Dental hygienist</td>
<td>Acacia</td>
</tr>
<tr>
<td>Herbal tea processor</td>
<td>Herbal tea, sarsaparilla root, sanyak (Dioscorea batatas), Korean ginseng (Panax ginseng), tea plant dust (Camellia sinensis), chamomile (unspecified)</td>
<td>Guan</td>
<td></td>
</tr>
<tr>
<td>Herbalist</td>
<td>Liquorice roots ( Glycyrrhiza spp.), wonji (Polygala tenuifolia), herb material</td>
<td>Gum importer</td>
<td>Guar</td>
</tr>
<tr>
<td>Horticulture</td>
<td>Freesia (Freesia hybridis), paprika (Capsicum annuum), Brazil ginseng (Plukenetia volubilis)</td>
<td>Hairdresser</td>
<td>Gutta-percha</td>
</tr>
<tr>
<td><strong>VEGETABLE GUMS</strong></td>
<td></td>
<td>Printer</td>
<td>Ttragacanth</td>
</tr>
<tr>
<td><strong>PLANT-DERIVED NATURAL PRODUCTS</strong></td>
<td></td>
<td></td>
<td>Karaya</td>
</tr>
<tr>
<td>Baker</td>
<td>Gluten, soybean lecithin</td>
<td>Vegetable</td>
<td>Acacia</td>
</tr>
<tr>
<td>Candy maker</td>
<td>Pectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glove manufacturer</td>
<td>Latex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health professional</td>
<td>Latex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rose extraction</td>
<td>Rose oil</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BIOLOGIC ENZYMES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker</td>
<td>Fungal amylose, fungal amyloglucosidase and hemicellulase</td>
<td>Drug</td>
<td>Exposure to drugs in environment</td>
</tr>
<tr>
<td>Cheese producer</td>
<td>Various enzymes in rennet production (proteases, pepsine, chymosines)</td>
<td>Dental hygienist</td>
<td>Pharmaceutical workers</td>
</tr>
<tr>
<td>Detergent industry</td>
<td>Esterase, Bacillus subtilis</td>
<td>Gum importer</td>
<td>Farmers</td>
</tr>
<tr>
<td>Factory worker</td>
<td>Bacillus subtilis</td>
<td>Hairdresser</td>
<td>Healthcare workers</td>
</tr>
<tr>
<td>Fruit processor</td>
<td>Pectinase and glucanase</td>
<td>Pharmaceutical</td>
<td>Laboratory work</td>
</tr>
<tr>
<td>Hospital personnel</td>
<td>Empyrase (pronase B)</td>
<td>Tobacco leaf</td>
<td>Healthcare professionals</td>
</tr>
<tr>
<td>Laboratory worker</td>
<td>Xylanase, phytoase from Aspergillus niger</td>
<td>Tobacco leaf</td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>METALS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laborer</td>
<td>Citrus food handling (dl-limonene, l-citronnellol, and dichlorophen)</td>
<td>Chemical</td>
<td>Workers/hobbyists</td>
</tr>
<tr>
<td>Oil industry</td>
<td>Castor bean, olive oilcake</td>
<td>Manufacturing</td>
<td>Sawmill</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>Rose hip, passion flower (Passiflora alata), cascara sagrada (Rhamnus purshiana)</td>
<td>Painters/hobbyists</td>
<td>Carpenter</td>
</tr>
<tr>
<td><strong>LOW MOLECULAR WEIGHT CHEMICALS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Powder</td>
<td>Lycopersicum powder</td>
<td>Environmental</td>
<td>Woodwork</td>
</tr>
<tr>
<td>Sewer</td>
<td>Kapok</td>
<td></td>
<td>Oak</td>
</tr>
<tr>
<td>Sheller</td>
<td>Almond shell dust</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stucco handler</td>
<td>Esparto (Stipa tenacissima and Lygeum spartum)</td>
<td>Exposure in the healthcare field</td>
<td></td>
</tr>
<tr>
<td>Tobacco manufacturer</td>
<td>Tobacco leaf</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 399-6  Low Molecular Weight Chemicals Known to Induce Occupational or Environmental Asthma

<table>
<thead>
<tr>
<th>CHEMICALS</th>
<th>OCCUPATION OR ENVIRONMENT SOURCE</th>
<th>CHEMICALS</th>
<th>OCCUPATION OR ENVIRONMENT SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diisocyanates</td>
<td>Polyurethane, Roofing materials, Insulations, Paint</td>
<td>Metals</td>
<td>Chromic acid, Potassium dichromate, Nickel sulfate, Vanadium, Platinum salts</td>
</tr>
<tr>
<td>Diphenylmethane</td>
<td>Paint</td>
<td>Drugs</td>
<td>β-Lactams, Opioids, Other</td>
</tr>
<tr>
<td>Hexamethylene</td>
<td>Paints, Epoxy resins</td>
<td>Chemicals</td>
<td>Formaldehyde, Glutaraldehyde, Ethylene oxide</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Personal or business use of dyes</td>
<td>Chemicals</td>
<td>Exposure in the healthcare field</td>
</tr>
<tr>
<td>Toluene</td>
<td>Hair dye, Fur dye, Fabric dye</td>
<td>Chemicals</td>
<td>Laboratory work, Healthcare professionals</td>
</tr>
<tr>
<td>Anhydrides</td>
<td>Manufacturers or users</td>
<td>Exposures</td>
<td>Workers/hobbyists, Sawmill, Carpenter, Woodwork</td>
</tr>
<tr>
<td>Trimellitic</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Workers/hobbyists, Sawmill, Carpenter, Woodwork</td>
</tr>
<tr>
<td>Phthalic</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Workers/hobbyists, Sawmill, Carpenter, Woodwork</td>
</tr>
<tr>
<td>Dyes</td>
<td>Personal or business use of dyes</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Anthraquinone</td>
<td>Hair dye</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Carmine</td>
<td>Fur dye</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Henna</td>
<td>Fabric dye</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Persulfate</td>
<td>Plastic</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Glue or resin</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Exposure to drugs in environment</td>
</tr>
<tr>
<td>Methacrylate</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Pharmaceutical workers</td>
</tr>
<tr>
<td>Acrylates</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Farmers, Healthcare workers</td>
</tr>
<tr>
<td>Epoxy</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Exposure in the healthcare field</td>
</tr>
<tr>
<td>Wood dust</td>
<td>Western red cedar (plicatic acid)</td>
<td>Chemicals</td>
<td>Laboratory work, Healthcare professionals</td>
</tr>
<tr>
<td>Exotic woods</td>
<td>Maple, Oak</td>
<td>Chemicals</td>
<td>Laboratory work, Healthcare professionals</td>
</tr>
<tr>
<td>Grain dust</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Laboratory work, Healthcare professionals</td>
</tr>
<tr>
<td>Diisocyanates</td>
<td>Polyurethane, Roofing materials, Insulations, Paint</td>
<td>Metals</td>
<td>Chromic acid, Potassium dichromate, Nickel sulfate, Vanadium, Platinum salts</td>
</tr>
<tr>
<td>Hexamethylene</td>
<td>Paint</td>
<td>Drugs</td>
<td>β-Lactams, Opioids, Other</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Paints, Epoxy resins</td>
<td>Chemicals</td>
<td>Formaldehyde, Glutaraldehyde, Ethylene oxide</td>
</tr>
<tr>
<td>Toluene</td>
<td>Personal or business use of dyes</td>
<td>Chemicals</td>
<td>Exposure in the healthcare field</td>
</tr>
<tr>
<td>Anhydrides</td>
<td>Manufacturers or users</td>
<td>Exposures</td>
<td>Workers/hobbyists, Sawmill, Carpenter, Woodwork</td>
</tr>
<tr>
<td>Trimellitic</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Workers/hobbyists, Sawmill, Carpenter, Woodwork</td>
</tr>
<tr>
<td>Phthalic</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Workers/hobbyists, Sawmill, Carpenter, Woodwork</td>
</tr>
<tr>
<td>Dyes</td>
<td>Personal or business use of dyes</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Anthraquinone</td>
<td>Hair dye</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Carmine</td>
<td>Fur dye</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
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<tr>
<td>Henna</td>
<td>Fabric dye</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Persulfate</td>
<td>Plastic</td>
<td>Metal work</td>
<td>Metalwork, Plating, Welding</td>
</tr>
<tr>
<td>Glue or resin</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Exposure to drugs in environment</td>
</tr>
<tr>
<td>Methacrylate</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Pharmaceutical workers</td>
</tr>
<tr>
<td>Acrylates</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Farmers, Healthcare workers</td>
</tr>
<tr>
<td>Epoxy</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Exposure in the healthcare field</td>
</tr>
<tr>
<td>Wood dust</td>
<td>Western red cedar (plicatic acid)</td>
<td>Chemicals</td>
<td>Laboratory work, Healthcare professionals</td>
</tr>
<tr>
<td>Exotic woods</td>
<td>Maple, Oak</td>
<td>Chemicals</td>
<td>Laboratory work, Healthcare professionals</td>
</tr>
<tr>
<td>Grain dust</td>
<td>Plastic</td>
<td>Chemicals</td>
<td>Laboratory work, Healthcare professionals</td>
</tr>
</tbody>
</table>
Reactive Airways Disease Syndrome and Irritant-Induced Asthma

RADS presents with the development of acute respiratory symptoms within minutes or hours following a single inhalation of a high concentration of irritant gas, aerosol, or smoke. Table 399-7 lists the criteria for diagnosis of RADS. Asthma-like symptoms and airway hyperresponsiveness then ensue, which often persist for prolonged periods. Unlike typical asthma, RADS is often not reversible by use of a bronchodilator. This is probably a consequence of the direct injury to the epithelium and subsequent submucosal fibrosis. Chlorine gas, acetic acid, dimethylaminoethanol, chlorofluorocarbons, epichlorohydrin, and diisocyanates have been studied by experimental design of comparative groups or epidemiology studies.

Irritant induced asthma is a closely related form of asthma resulting from nonimmunologic provocation of bronchial hyperresponsiveness with airflow obstruction induced by irritant chemicals in low concentration after single or multiple exposures. If the resultant pulmonary symptoms occur after multiple exposures at a plant, it is termed nonimmunologic-induced asthma.

Predisposing factors for the development of RADS are not well characterized. Atopy and cigarette smoking may increase the risk of developing RADS when exposure through inhalation of irritant chemicals occurs. In addition to host factors, the type of chemical appears to be important. Higher concentrations of chemicals, the type of chemical (vapor or wet aerosols), and bleaching agents are the most offending agents to cause RADS. Dry particle aerosols are less likely to cause RADS. Analysis of the World Trade Center firefighters indicates that the presence of bronchial hyperresponsiveness prior to a chemical exposure does not increase the risk for an individual to develop RADS.

Pathogenesis of RADS follows a typical pattern. Initial histology demonstrates rapid denudation of the mucosa accompanied by submucosal fibrous, hemorrhagic exudate. Subepithelial edema occurs subsequently with some regeneration of the epithelial layer, proliferation of basal and parabasal cells, and eventually areas of fibrosis. The desquamation, subepithelial fibrosis, thickening of the basement membrane, and regeneration of basal cells are all more prominent in RADS than in occupational asthma. This may explain the limited response to bronchodilator therapy in this syndrome compared to asthma.

The clinical manifestations of RADS and irritant-induced asthma are different from each other mostly in the onset of symptoms. Patients with RADS typically can pinpoint the exact time of onset of symptoms as well as the exact number of hours postexposure. The symptoms are so severe that nearly 80% of subjects in one study presented to an emergency department for care. The lower airway symptoms of cough, dyspnea, chest tightness, and wheezing are prominent features in RADS, with cough being most prevalent. Because of the toxic nature of the inhaled chemical, it is predictable that an upper airway syndrome of throat and nose burning will often accompany the lower airway symptoms. This part of the complex has been referred to as respiratory upper airway dysfunction syndrome.

Individuals with irritant-induced asthma present with a more insidious onset of symptoms. Because of the recurrent nature of the low concentration of chemical, patients may not be able to identify the underlying trigger initially. Similar to allergic rhinitis, patients may describe nasal congestion, rhinorrhea, sneezing, postnasal drip, ocular irritation, and conjunctival injection. Pulmonary symptoms include those typically seen with asthma exacerbations.

Initial evaluation of the patient with RADS or irritant-induced asthma usually includes the medical history, physical examination, and pulse oximetry. Because of the acute nature of RADS, a chest radiograph is obtained in order to rule out other acute causes of dyspnea including pneumonia or pulmonary edema. Ideally, if the patient is not in significant distress, complete pulmonary functions with spirometry, lung volumes, and diffusion capacity are very helpful in the initial evaluation. The lack of abnormality on initial chest radiograph reassures the clinician that HRCT is not indicated.

### Table 399-7: Criteria for the Diagnosis of Reactive Airways Disease Syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of previous documented respiratory symptom</td>
<td></td>
</tr>
<tr>
<td>Onset of symptoms most often occur after a single specific exposure</td>
<td></td>
</tr>
<tr>
<td>Exposure is most often to a high concentration of gas, smoke, fume, or vapor with irritant qualities</td>
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<tr>
<td>Symptoms occur within 24 hr of exposure and persist for 3 mo or longer</td>
<td></td>
</tr>
<tr>
<td>Symptoms mimic asthma with cough, wheezing, shortness of breath, and/or dyspnea</td>
<td></td>
</tr>
<tr>
<td>Pulmonary function tests may demonstrate airflow obstruction but not always</td>
<td></td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness is documented by methacholine challenge</td>
<td></td>
</tr>
<tr>
<td>Alternative pulmonary diseases are not able to be found</td>
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</tr>
</tbody>
</table>

### 399.3 Granulomatous Lung Disease

Kevin J. Kelly

**GRANULOMATOSIS WITH POLYANGIITIS**

Granulomatosis with polyangiitis (GPA) is a disease that involves both the lower and upper respiratory tracts with granulomatous inflammation of small vessels; formerly it was known as Wegener granulomatosis (see Chapter 167). The pulmonary disease is frequently associated with glomerulonephritis. The simultaneous presence of pulmonary and renal disease should immediately raise the suspicion that either GPA or Goodpasture disease (see Chapter 399.5) may be causing the disease.

**Etiology and Epidemiology**

The prevalence of GPA disease appears to be increasing by up to 4-fold in the last 2 decades, but without male or female predominance. Diagnostic tests, such as antineutrophil antibodies, may explain some of this increased prevalence.

**Pathogenesis**

Clinically, the development of both upper and lower airway disease with granulomas in GPA implies that exposure to antigen in the airway of endogenous or exogenous source is involved with aberrant cell-mediated immune response. Cytokine expression by peripheral blood CD4+ lymphocytes and cells collected by BAL indicate there is a predominantly T-lymphocyte type 1 response with overexpression of interferon-γ (IFN-γ) and tumor necrosis factor (TNF). In vitro studies demonstrate a skewed T-lymphocyte type 17 response by blood CD4+ T cells in GPA, suggesting there is an immune regulatory defect that leads to excessive production of T-lymphocyte type 1/T-lymphocyte type 17 cytokines (interleukin [IL]-17, TNF, and IFN-γ) presumed to be from the environment or autoantigens. Such an inflammatory response may be sufficient to induce and sustain granuloma formation.
Bibliography

Detection of autoantibodies reactive against proteins in the cytoplasmic granules of neutrophils and monocytes (antineutrophil cytoplasmic antibodies [ANCAs]) are found in 90% of the patients with GPA. The first major type of ANCA is directed against cytoplasmic proteinase-3 and is frequently named c-ANCA. The second major type of ANCA recognizes the enzyme myeloperoxidase. It is found in a small number (<10%) of patients with GPA. Antimyeloperoxidase antibodies fluoresce in a perinuclear pattern and are often referred to as perinuclear ANCA. In contrast, some patients develop the clinical phenotype of GPA in the absence of detectable ANCA.

**Clinical Manifestations**
Children with GPA present with respiratory complaints accompanied by fever, loss of energy, and vague joint complaints. Some may present with severe nasal disease manifested as ulceration, septal perforation, pain, sinusitis, and or epistaxis. The septal perforation may lead to deformation of the nasal bridge from erosion of the underlying cartilage but is more common in adults. Pulmonary disease occurs in the majority of patients as noted above. Symptoms range from cough, hemoptysis, dyspnea, and chest discomfort to asymptomatic infiltrates on chest radiography. Occasionally, patients with GPA will present with hemoptysis or recurrent fleeting infiltrates from pulmonary hemorrhage. The pathology is confusing because granulomatous disease may be difficult to demonstrate and can be confused with microscopic polyangiitis. This is found most frequently in Goodpasture disease, microscopic polyangiitis, and Henoch-Schönlein purpura. Distinguishing GPA from other pulmonary renal syndromes is easiest when there are classical symptoms of upper airway disease (nasal/sinus), lower airway disease with necrosis, granulomas on biopsy of the lung with vasculitis, and renal disease consistent with glomerulonephritis.

As many as 20% of patients with GPA will present with subglottic or endobronchial stenosis from scarring and inflammatory changes. Although it may be the presenting symptom, it often occurs in conjunction with other disease manifestations. Dyspnea and voice changes are common complaints from the patients.

Skin, ocular, and joint symptoms are common in GPA and have been found to accompany the lung and renal disease in most series 50% or more of the time. Biopsy of the skin may show nonspecific leukocytoclastic vasculitis, venulitis, or capillaritis.

**Laboratory and Pathology**
c-ANCA or anti–proteinase-3 antibodies are found in 90% of patients with GPA. However, they are also found in other types of vasculitis and are not sufficient in themselves to make a diagnosis without a tissue biopsy (see Chapter 167). Because of the necrotizing nature of the vasculitis, lung tissue is required for definitive diagnosis of pulmonary disease. Biopsy of the upper airway may demonstrate evidence of granulomatous disease but it is uncommon to find evidence of vasculitis; lung biopsy is warranted. Usual pathology demonstrates multiple parenchymal nodules that may be located in either the bronchial, vascular, or interstitial tissues (Fig. 399-2). The granulomatous inflammation often is found areas of necrosis and/or vasculitis.

Renal biopsy rarely is able to demonstrate granulomas or vasculitis. Rather, kidney tissues may show focal, segmental, or necrotizing glomerulonephritis without deposits of immune complexes. When the tissues fail to demonstrate classical findings, a variety of diseases (e.g., tuberculosis, sarcoid, microscopic polyangiitis, malignancy, and other autoimmune disorders) must be considered in the evaluation.

**Radiology**
Chest radiography in GPA will show multiple infiltrates, nodules, cavitary lesions, or interstitial lung disease. Fleeting infiltrates may be seen when recurrent hemorrhage is a part of the clinical manifestation. HRCT often demonstrates more extensive lung disease and the cavitation associated with the necrotizing nature of the disease (Fig. 399-3).

**Treatment**
Rapidly progressive, debilitating disease may occur when failure to diagnose GPA leads to inadequate treatment. One series of patients showed death occurred in 90% of patients within 2 yr of diagnosis. Glucocorticoid therapy alone resulted in relapses and inadequate control of disease in many subjects. Standard initial induction of therapy includes prednisone at 1 mg/kg/day in combination with oral cyclophosphamide at 2 mg/kg/day or intravenous dosing at 15 mg/kg.
more likely to be asymptomatic with a more chronic disease. There is evidence that African-American females are disproportionately affected more than males. In that setting, up to 50% of diagnosed sarcoidosis is asymptomatic. The severity of the disease appears to be worse in African-American females than in males. Epidemiology and Pathogenesis

Sarcoidosis is an idiopathic inflammatory disease involving multiple organ systems, with characteristic histology of noncaseating granulomas (see Chapter 165). It has been postulated that sarcoidosis represents an immune response to a yet-to-be-identified agent from the environment that is likely inhaled in a susceptible host. It remains a diagnosis of exclusion from other diseases with granuloma formation on histology, such as immune deficiency of chronic granulomatous disease, granulomatous lymphocytic interstitial lung disease associated with common variable immune deficiency, HP with associated some drugs and inhalation agents, granuloma with polyangiitis, typical and atypical Mycobacterium, Pneumocystis jiroveci, and malignancy.

**Clinical Manifestations**

Patients with lung disease are more likely to be asymptomatic as the presentation often may be an abnormal chest radiograph. When symptomatic, patients demonstrate shortness of breath, cough, and dyspnea. Children are more likely to manifest the disease as iridocyclitis, skin rash, and arthritis. African-American children appear to have more frequent lymph node involvement, nonspecific elevations of gamma globulin, erythema nodosum, and hypercalcemia. Physical exam may reveal only an elevated respiratory rate without crackles or rales by auscultation. Pleural involvement has been seen but is uncommon. When present, a lymphocytic predominant exudate may be observed with laboratory evaluation of the pleural fluid. Unusual but reported findings include cases of pneumothorax, hemoptoex, and chylothorax. One specific syndrome, Lofgren syndrome, with hilar lymphadenopathy, erythema nodosum, and migratory polyarthralgias, is almost exclusively seen in women. This syndrome has a strong association with HLA-DQB1*0201 and polymorphisms in the C-C chemokine receptor 2 (CCR2); these genetic markers are a predictor of a good outcome.

Although almost 90% of patients with sarcoidosis demonstrate parenchymal or mediastinal disease on chest radiography, there are many who have minimal to no symptoms. Approximately 10% of adults with stage 1 disease have endobronchial involvement found at bronchoscopy. The higher the staging level of disease, the higher the percentage of people with airway involvement.

**Diagnostic Laboratory Testing**

The most common but nonspecific findings are hypergammaglobulinemia, hypercalciciuria, hypercalcemia, elevated alkaline phosphatase when liver disease is present, and, occasionally, anemia of chronic disease. Serum angiotensin-converting enzyme may be elevated in 75% of patients with untreated sarcoid. False-positive tests occur from other diseases so that it is not considered a diagnostic test but rather a test that strongly supports the diagnosis.

Pulmonary function tests are able to be performed accurately in most children older than the age of 4 yr. There are no specific diagnostic findings of spirometry, lung volumes, or diffusion capacity in sarcoidosis. Exercise coupled with pulmonary function tests may demonstrate a decline in diffusion capacity when alveolitis is present in hypersensitivity pneumonitis and could add diagnostic help to the clinician when attempting to differentiate sarcoidosis from HP prior to biopsy.

**BAL** is of great help when differentiating HP from sarcoid. BAL in sarcoid shows a marked predominance of CD4 cells. A lymphocyte

monthly. This regimen is effective at induction of remission of disease process. The advantage of oral daily dosing is a reduction in relapse of disease once induction has occurred. After induction of remission (usually in 3 mo), prednisone can be tapered to an every-other-day regimen and eventually discontinued in 6-8 mo. After induction of remission, cyclophosphamide should be discontinued because of drug toxicity, serious risk of infections, risk of infertility, or cancer. In those patients with recurring relapse, cyclophosphamide has had limited use.

Once remission was achieved and cyclophosphamide discontinued; both methotrexate and azathioprine demonstrated efficacy with lowered side effects during maintenance of remission therapy for approximately 1 yr. Adjuvant therapy with plasma exchange may be considered when life-threatening GPA disease presents. This is advocated on the premise that ANCA are inducing disease and will be removed from the circulation with this intervention; its use has been favorably evaluated in GPA-induced renal disease. Plasmapheresis and exchange is advocated as adjuvant treatment for severe manifestations of GPA and related ANCA-associated disease based on the theoretical benefit of removing potentially pathogenic ANCA. Adjuvant plasma exchange has been studied mainly in patients with severe renal vasculitis, but there are also reports of success in severe pulmonary hemorrhage. The results of a meta-analysis of patients with renal vasculitis in 9 trials, suggest that adjuvant plasma exchange may be associated with improved renal outcome.

The removal of B-cells that produce ANCA may be effective by reducing the production of pathogenic antibodies. Rituximab, an anti-CD20 chimeric antibody, regimens used in conjunction with glucocorticoids or glucocorticoids with a short course of cyclophosphamide are equally efficacious in inducing remission when compared to more prolonged therapy with steroid plus cyclophosphamide.

Recurrence disease remains a major problem. ANCA levels have not been shown to correlate with activity of disease or severity. Patients who are treated for the sinesuses and nose may not warrant such toxic therapy. Therapy with topical corticosteroid and antibiotics for infection appear to be warranted. If unsuccessful, steroid with methotrexate appears to be an effective therapy.

The development of subglottic stenosis requires specific treatment. Use of cyclophosphamide with oral corticosteroid may have an incomplete or no response in the airway. Local injection of a prolonged acting corticosteroid locally appears to be indicated to reduce the inflammation and prevent further scarring. If this complication is found at presentation, simultaneous airway intervention with induction of corticosteroid and cyclophosphamide is warranted and encouraged.

**SARCOIDOSIS**

Sarcoidosis is an idiopathic inflammatory disease involving multiple organ systems, with characteristic histology of noncaseating granulomas (see Chapter 165). It has been postulated that sarcoidosis represents an immune response to a yet-to-be-identified agent from the environment that is likely inhaled in a susceptible host. It remains a diagnosis of exclusion from other diseases with granuloma formation on histology, such as immune deficiency of chronic granulomatous disease, granulomatous lymphocytic interstitial lung disease associated with common variable immune deficiency, HP associated with some drugs and inhalation agents, granuloma with polyangiitis, typical and atypical Mycobacterium, Pneumocystis jiroveci, and malignancy.

**Epidemiology and Pathogenesis**

African-American females are disproportionately affected more than any other group. Because an asymptomatic sarcoid-like distribution of noncaseating granulomas may be frequently found at autopsy, the contribution of the granulomas to the disease is not always clear. Some countries do mass chest radiograph screening for multiple diseases. In that setting, up to 50% of diagnosed sarcoidosis is asymptomatic. The severity of the disease appears to be worse in African-Americans who tend to have acute illness, whereas white subjects are more likely to be asymptomatic with a more chronic disease. There have been clusters of disease in families and genetic testing suggests that MHC linkage on the short arm of chromosome 6 is most likely to be observed.

Sarcoidosis is rarely found in children younger than the age of 8 yr; those of African descent are most affected. The disease presentation is similar to adults with multisystem disease being the most common. Skin rash, iridocyclitis, and arthritis are seen most often without pulmonary symptoms. In northern Europe, erythema nodosum with the ocular involvement of iridocyclitis is seen most frequently. Despite the lack of symptoms, chest radiography may be abnormal in approximately 90% of children. The pulmonary disease appears to be less progressive compared to adults and patients recover spontaneously without corticosteroids. Rarely, pulmonary disease may progress to fibrosis. Ocular disease is more likely to be progressive and warrant intervention as the inflammatory response may lead to blindness from complications of iritis.

Unrecognized infection or inhalation of an immune response-inducing antigen continues to be at the forefront of consideration as a cause of the disease. Clusters of sarcoidosis in small populations, variable prevalence by geography and race, transfer of disease by organ transplant, and the reproducible granuloma formation only in patients with sarcoidosis in the skin when homogenized lymph node tissue from patients with sarcoid are injected intradermally (Kveim-Siltzbach test) have supported this hypothesis.

**Clinical Manifestations**

Patients with lung disease are more likely to be asymptomatic as the presentation often may be an abnormal chest radiograph. When symptomatic, patients demonstrate shortness of breath, cough, and dyspnea. Children are more likely to manifest the disease as iridocyclitis, skin rash, and arthritis. African-American children appear to have more frequent lymph node involvement, nonspecific elevations of gamma globulin, erythema nodosum, and hypercalcemia. Physical exam may reveal only an elevated respiratory rate without crackles or rales by auscultation. Pleural involvement has been seen but is uncommon. When present, a lymphocytic predominant exudate may be observed with laboratory evaluation of the pleural fluid. Unusual but reported findings include cases of pneumothorax, hemoptoex, and chylothorax. One specific syndrome, Lofgren syndrome, with hilar lymphadenopathy, erythema nodosum, and migratory polyarthralgias, is almost exclusively seen in women. This syndrome has a strong association with HLA-DQB1*0201 and polymorphisms in the C-C chemokine receptor 2 (CCR2); these genetic markers are a predictor of a good outcome.

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**Diagnostic Laboratory Testing**

The most common but nonspecific findings are hypergammaglobulinemia, hypercalciciuria, hypercalcemia, elevated alkaline phosphatase when liver disease is present, and, occasionally, anemia of chronic disease. Serum angiotensin-converting enzyme may be elevated in 75% of patients with untreated sarcoid. False-positive tests occur from other diseases so that it is not considered a diagnostic test but rather a test that strongly supports the diagnosis.

Pulmonary function tests are able to be performed accurately in most children older than the age of 4 yr. There are no specific diagnostic findings of spirometry, lung volumes, or diffusion capacity in sarcoidosis. Exercise coupled with pulmonary function tests may demonstrate a decline in diffusion capacity when alveolitis is present in hypersensitivity pneumonitis and could add diagnostic help to the clinician when attempting to differentiate sarcoidosis from HP prior to biopsy.

**BAL** is of great help when differentiating HP from sarcoid. BAL in sarcoid shows a marked predominance of CD4 cells. A lymphocyte...
percentage >16% on BAL, a CD4:CD8 ratio >4, and noncaseating granulomas on bronchial biopsy in the presence of abnormal angiotensin-converting enzyme levels are nearly completely diagnostic for sarcoid. In addition, T cells are activated on BAL. BAL in HP shows a significant change in the balance of CD4 to CD8 cells with the 2 cell types being nearly equal compared to the normal mild predominance of CD4 cells in the circulation. A ratio of CD4:CD8 of <1 predicts 100% of patients with BAL lymphocytosis to not have sarcoidosis. Neutrophil counts >2% and/or eosinophil counts >1% exclude the diagnosis of sarcoidosis.

The analysis of D-dimers in BAL fluid from subjects with sarcoidosis demonstrates an elevation in 80% of patients compared to no detectable D-dimers in unaffected control.

**Histopathology**

The characteristic feature of sarcoidosis is the noncaseating granuloma formation in the lung (Fig. 399-4). These granulomas are found in the bronchial walls, alveolar septa, and vascular walls of pulmonary arteries and veins. The formation of noncaseating granulomas is likely preceded by alveolitis involving the interstitium more than the alveolar spaces. There is accumulation of inflammatory cells, including monocytes, macrophages, and lymphocytes that accompany the granulomas. Multinucleated giant cells are frequently found among the epithelioid macrophages, lymphocytes, and eosinophils that make up the granulomas. These are most often identified in the upper lobes of the lungs, which may lead to confusion with diseases such as hypersensitivity pneumonitis, eosinophilic granuloma, collagen vascular disease, pneumocystis, berylliosis, and infectious disease such as tuberculosis or histoplasmosis.

**Radiology**

Pulmonary imaging in sarcoid has included plain chest radiography, HRCT, positron emission tomography using fluorine-18-fluorodeoxyglucose, and radiotracer using gallium-67. The staging of sarcoid is performed using plain radiography and is outlined as follows:

- **Stage I**—Bilateral hilar lymphadenopathy accompanied by right paratracheal lymphadenopathy
- **Stage II**—Bilateral hilar lymphadenopathy accompanied by reticular opacities are present. If symptomatic, patients have cough and dyspnea. Occasional fever and fatigue accompany the respiratory symptoms.
- **Stage III**—Reticular opacities are found predominantly in the upper lobes with regression of hilar lymphadenopathy.

- **Stage IV**—Reticular opacities start to coalesce and lead to volume loss in the lung fields, traction bronchiectasis from conglomerations of the inflamed tissues. Extensive calcium deposits may be seen at this stage.

HRCT may be helpful in further staging of the disease, as well as in revealing abnormalities not appreciated on chest radiography. Findings in patients with sarcoidosis by HRCT include hilar lymphadenopathy, paratracheal nodules, middle to upper lung parenchymal ground-glass appearance, bronchial wall thickening, bronchiectasis, cystic changes, and fibrosis. The ground-glass appearance suggests that alveolitis, as seen in hypersensitivity pneumonitis, may be present. Biopsy has usually shown granuloma formation as the predominant histologic finding.

**Treatment**

Because pulmonary sarcoidosis spontaneously resolves without therapy in almost 75% of patients, clear guidelines for treatment focused on minimizing side effects of therapy is required. Glucocorticosteroids (GCSs) have long been the mainstay of therapy in sarcoid and are often used because of extra pulmonary disease. When pulmonary disease is progressive, GCS therapy is aimed at prevention of fibrosis, honeycombing, and irreversible lung disease. Assuring that disseminated infections, heart failure, thromboembolism, or pulmonary hypertension are not present is important. In addition to HRCT of the chest, performance of pulmonary function tests, electrocardiogram and echocardiogram should be considered prior to starting GCS therapy.

GCS therapy is often not started when stage I or II is present without symptoms. This scrutiny of the benefit of therapy was highlighted when prospective evaluation of GCS therapy for pulmonary disease found that nearly 50% of patients receiving GCSs had active or relapsing disease 2 yr later. In contrast, 90% of patients who did not receive GCSs had spontaneous remission of disease with the other 10% needing intervention 2 yr later. Absolute indications include progressive stage III disease with symptoms of shortness of breath, cough, or other chest symptoms such as pain. Progressive restriction shown on pulmonary function testing is an indication for therapy. Specific pulmonary function changes where lung capacity declines total 10% or greater, forced vital capacity declines 15% or more, or diffusion capacity degradation is seen of 20% or more are all indications for GCS intervention.

Dosage with oral prednisone at 0.3–0.5 mg/kg is a reasonable starting point depending on the severity of symptoms. Stability is usually achieved within 6–8 wks, after which slow progressive tapering of GCS may occur every 4–8 wks. Many favor the use of alternate-day steroids to reduce the side effects of GCSs, but little data exist to show efficacy.
Patients who do not tolerate GCSs or develop progressive disease, alternative immunosuppressive agents may add benefit to the regimen. Progressive disease also is a reminder for the clinician to reassess the diagnosis of sarcoid and review the chance that beryllium may have been the underlying reason for the progressive disease.

Inhaled GCSs have been evaluated in patients with stage I disease with variable results. Evaluation of therapy with pulmonary function testing and symptoms are the best methods to judge responsiveness to this therapy. Persistent symptoms after 4-8 wks of therapy suggest that systemic GCSs may be indicated.

**BERYLLIOSIS**

Chronic beryllium disease or berylliosis is an example of environmental exposure and unique granulomatous response in the lungs. Beryllium is an alkaline metal that is used in a number of industrial settings.

A diagnosis of berylliosis requires 3 criteria: (1) history of beryllium exposure; (2) positive response to lymphocyte proliferation tests to beryllium in lymphocytes obtained by BAL or blood test; and (3) noncaseating granulomas on lung biopsy. Exposure to beryllium may occur in industries such as automotive, ceramic, aerospace, metal extraction, electronics, computer, jewelry making, and dental alloys. Teenagers working summer jobs in machine work, ceramics, or wire production may be exposed. Sensitization is associated with dose and duration of exposure and has been seen to be as high as 20% in certain industries. Secretaries working in buildings where manufacturing with beryllium is active have developed berylliosis.

**Pathogenesis**

Genetic susceptibility coupled with immunologic response to beryllium are the 2 key contributors to the development of disease. A T-lymphocyte cell–mediated delayed hypersensitivity response to beryllium appears to be the mechanism involved with granuloma formation in the lung. The lymphocyte proliferation by T cells to beryllium is specific and does not occur to other metals. Similar to sarcoidosis, CD4+ T cells predominate on bronchoalveolar response. Beryllium appears to be inhaled and then couple with proteins in the lung or can be ingested by antigen-presenting cells. The cytokines elicited and granuloma formation suggests that sensitization is primarily a T-lymphocyte type 1 response with elevated interferon-γ and IL-2 production.

**Clinical Manifestations**

The clinical manifestations of berylliosis are not specific. Dry cough, fever, fatigue, weight loss, and shortness of breath all may be present. Although symptoms may occur within 3 mo, new disease has been detected up to 3 decades after exposure. Physical examination is somewhat different than the HPs and sarcoid with bibasilar crackles found on auscultation. The other mentioned diseases are more prominent in the upper lobes. Small nodule on exposed skin may also be present.

**Laboratory Testing**

Suspicion of berylliosis should prompt the clinician to have blood lymphocyte proliferation studies to beryllium performed as well as complete pulmonary functions. These tests need to be sent to a special center where multiple tests are run with comparison to positive proper and negative controls. When positive, the test has very high specificity for defining the presence of berylliosis at approximately 96%. However, sensitivity of the test hovers at <70%, suggesting that approximately 3 of every 10 patients who have disease may have a negative test.

Similar to other pulmonary granulomatous diseases, increased production of calcitriol is commonly found. The source of this active form of vitamin D is from activated pulmonary macrophages, which may result in hypercalcemia and hypercalciuria.

**Radiography**

Chest radiographs should be obtained on all patients suspected of having berylliosis. The chest radiograph may be normal, show hilar lymphadenopathy, pulmonary nodules, ground glass, or alveolar opacities. The parenchymal abnormalities may be diffuse or may be more prominent in the upper lobes. These findings are dependent upon the stage of the disease.

HRCT is the most sensitive test in the identification of chronic berylliosis. Almost 25% of the HRCT exams in patients with biopsy proven berylliosis are found to be normal. Similar to other granulomatous and HPs of the lungs, HRCT findings include parenchymal nodules of varying size, thick septal lines, ground-glass opacities, cystic cavituation, and lymphadenopathy in the hilum or mediastinum. Pleural abnormalities are less common, but thickening may be observed in proximity to parenchymal nodules.

**Treatment**

Managing berylliosis involves avoiding further exposure and therapy with glucocorticoids or other immunosuppressive agents. A decision to intervene depends on the severity of symptoms, physiologic impairment based on pulmonary function tests, and extent of radiographic changes. Treatment is usually started when the patient has dyspnea or cough, >10% decline in lung volumes or gas exchange, or abnormal pulmonary function tests at baseline.

Small case series have demonstrated efficacy of steroids judged by improvement of clinical symptoms, radiographic clearing of disease, and improvement in pulmonary functions, including diffusion capacity. Some patients despite improved symptoms have recurrence which may progress to fibrosis and persistent lung disease.

The differentiation between berylliosis and sarcoidosis appears to be important for long-term outcomes. It appears that the longer the delay in prescribing GCSs to patients with berylliosis may lead to a state where the lung disease is unresponsive to therapy. In contrast, use of steroids may lead to a higher rate of recurrent disease. What makes the 2 responses different is not known.

Dosing of steroids is similar to sarcoid with a starting dose of 0.5 mg/kg/day of prednisone for a duration of 6-12 wks. Once a response is established, conversion to every-other-day corticosteroid use at the same dose followed by tapering should be attempted until the lowest dose is achieved that controls the disease. Patients may require persistent therapy for the rest of their life. Genetic susceptibility to the disease may predict relapse of disease. Mutations in the HLA-DPB1 gene (homozygous for glutamate substitution at the β69 position) appear to predict specific patients who are susceptible to relapse of symptoms.

When patients fail to respond or experience recurrent relapse, methotrexate in low dose has conferred a favorable response in some patients as has been seen with sarcoidosis. Azathioprine may also be considered since sarcoidosis has responded favorably, however there are no published trials using this immunosuppressive agent. A small number of cases have also shown promise with TNF-α inhibitors both in sarcoid and beryllium-induced disease.

**GRANULOMATOUS LUNG DISEASE IN PRIMARY IMMUNE DEFICIENCY**

**Primary immune deficiency (PIDD)** is often presents with recurrent or persistent pulmonary symptoms of recurrent infections, pneumonia, bronchiectasis, and interstitial lung disease with or without fibrosis. Immune dysregulation occurs in many of the PIDD with development of granulomatous lung disease and autoimmune disease. Most effort is focused on discovery of infectious pathogens in the PIDD causing pulmonary disturbance, but the dysregulation may be the primary problem causing symptoms and disease progression. This requires counterintuitive therapies with suppression of the immune system concurrently with immune deficiency therapy. The 2 most prominent PIDD associated with granulomatous lung disease are chronic granulomatous disease (CGD) (see Chapter 130) and common variable immune deficiency (CVID) (see Chapter 126).

The prototype organism causing granuloma formation in the lung is Mycobacterium tuberculosis. Nontuberculous mycobacterial infections also can cause granulomas in the presence of specific PIDD. These have been seen in impaired IL-12/IL-23/IFN-γ signaling, or the presence of autoantibodies to IFN-γ. Patients with defective regulation of nuclear factor-kappa B (nuclear factor-kappa B essential modifier defects) have
also been described as well with nontuberculous mycobacteria. The clinician must be certain that this low-virulence organism is not causing disease before therapy for immune dysregulation is considered.

Pathogenesis
CGD is a PID involving multiple defects in the phagocyte nicotinamide adenine dinucleotide phosphate oxidase system, which impairs the respiratory burst capacity to generate reactive species of oxygen (see Chapter 130). Up to 25% of patients with CVID develop lung disease (see Chapter 126). These pulmonary changes include organizing pneumonia, ILD, mucosa-associated lymphoid tissue lymphoma, and noncaseating granulomas in granulomatous and lymphocytic interstitial lung disease (GLILD). Elevated levels of TNF from TNF polymorphisms have been implicated as a possible mechanism. GLILD is becoming recognized more frequently in CVID. It is defined by the presence of granulomatous and a lymphocytic proliferative pattern in the lung. Granulomas may be found in other organs including bone marrow, spleen, gastrointestinal tract, skin, and liver.

The etiology of GLILD is unknown. In a case cohort study, a majority of subjects with pathology diagnostic of GLILD were found to have human herpesvirus 8 infection of the lung. These may represent a subgroup of patients with GLILD which may point to a mechanism underlying the development of pulmonary granulomas.

GLILD is sometimes misdiagnosed as sarcoidosis initially because both involve pulmonary granuloma, often accompanied by hilar and/or mediastinal lymphadenopathy. Sarcoidosis has several features that distinguish it from GLILD, such as normal or elevated serum immunoglobulin levels and frequent spontaneous remissions.

Clinical Manifestations of Granulomatous Lung Disease in Primary Immune Deficiency
Chronic respiratory disease as a result of recurrent infections is common in CGD. This is accompanied by clubbing in some patients and the other organ manifestations in the skin, liver, and gastrointestinmary and gastrointestinal tracts. Granulomas are especially problematic in the gastrointestinmary and genitourinary tracts. The inhalation of fungal spores and hyphae has led to an acute pneumonia in CGD with rapid progression to respiratory failure with hypoxemia, dyspnea, and fever. This entity, characterized as multich pneumonia, appears to be best treated with antifungal medications and corticosteroids.

Radiography
Hilar and/or mediastinal lymphadenopathy occur with granulomatous lung involvement. These may manifest as parenchymal nodules and/or ground glass abnormalities and can be seen commonly in CVID and CGD. Differentiating infectious causes of pulmonary infiltration in PID is often difficult on chest radiography; HRCT is often mandatory in the initial evaluation of the patients with CVID.

Laboratory and Pulmonary Function Testing
Definitive diagnosis is made by lung biopsy. Transbronchial biopsy in children is often insufficient and lung biopsy by video-assisted thoracoscopy or open biopsy is preferred. Unless the patient’s underlying immune deficiency is unknown, other laboratory testing except for infectious organisms does not contribute significantly to the diagnosis. When the child is old enough, complete pulmonary functions with spirometry, flow volume loop, lung volumes, and diffusion capacity should be obtained at baseline and then followed serially for response to therapy or progression of disease.

Therapy
The presence of GLILD in CVID can be associated with significant morbidity and possibly death. Without therapy, progressive pulmonary fibrosis and respiratory failure may occur in GLILD. The parenchymal disease may not always be controlled or relieved by glucocorticoid treatment. Other treatments include TNF antagonists, cyclosporine, or a combination therapy with rituximab and azathioprine. Response to therapy is monitored clinically and by interval HRCT of the chest, and pulmonary function testing, including spirometry, lung volumes, and diffusing capacity.

Bibliography is available at Expert Consult.

399.4 Eosinophilic Lung Disease
Kevin J. Kelly

The eosinophilic lung diseases are a group of heterogeneous pulmonary disorders with a predominant diffuse infiltration of eosinophils in the alveolar spaces or interstitial pulmonary spaces. Lung architecture is well preserved throughout the inflammatory response, often with complete reversal of the inflammation without long-term sequelae in the majority of cases. The peripheral white blood count often (but not always) reveals elevated eosinophils. Prompt recognition of the nature of these diseases allows for lifesaving interventions in the idiopathic acute eosinophilic pneumonia syndrome (AEP) or resolution of persistent symptoms in the patients with chronic disease.

Etiology
Eosinophilic lung diseases are often classified under 2 subheadings: idiopathic disease and known causation (Table 399-8). They are frequently further subdivided as acute and chronic or infectious and noninfectious. The division of acute or chronic is arbitrary based on the length of symptoms present (acute < 1 mo and chronic > 1 mo) but is relevant to the clinician in determining the etiology of the symptoms in the differential diagnosis. Löbländer eosinophilic pneumonia, induced by Ascaris lumbricoides and other ascarids, produces transient symptoms that self-resolve and is classified as neither acute nor chronic. Löbländer syndrome has been more correctly termed pulmonary infiltrates with eosinophilia syndrome and is the most common eosinophilic infiltrative disease in children.

Pathology and Pathogenesis
Eosinophilic lung disease, regardless of the stage of disease or etiology, shows mixed cellular infiltration of the alveoli and interstitial spaces with a predominance of eosinophils when transbronchial biopsy or open lung biopsy is performed. This may be accompanied by a fibrinous exudate with intact lung architecture. Other findings include eosinophilic microabscesses, a nonnecrotizing nongranulomatous vasculitis, and occasional multinucleated giant cells again without granuloma formation. BAL is the diagnostic procedure of choice, especially in the acute situation with the acute eosinophilic pneumonias; the differential cell count on the BAL is ≥25% eosinophils and is often more than 40%. This highly sensitive test and high specificity test has allowed clinicians to forego lung biopsy.

Eosinophils are filled with numerous toxic granules. Evidence of eosinophil degranulation may be found by electron microscopy, biopsy, urine excretion, and BAL fluid. Most commonly, eosinophil-derived neurotoxin, leukotriene E4, other granule proteins, such as major basic protein, Charcot Leyden crystals, or proinflammatory cytokines, are identified and support the evidence that eosinophils are not only present but contributing to the disease process.

Clinical Manifestations
Specific eosinophilic lung diseases present with a variable clinical picture; however, there are some common findings across many of the eosinophilic diseases. Dyspnea is the most common and prevalent symptom in patients with acute or chronic eosinophilic pneumonia and is accompanied by cough in the majority of patients (90%). Rhinitis and sinusitis symptoms are of lower prevalence with wide variability in children with eosinophilic pulmonary disease. Only the A specific disorder, acute eosinophilic pneumonia, consistently presents with respiratory failure and the requirement for mechanical ventilation at high levels of positive end expiratory pressure and high concentrations of oxygen. Although malignancy (e.g., eosinophilic leukemia) and organizing pneumonia may present with need for mechanical
Bibliography
ventilation, they are less common. A history of asthma is common in the chronic eosinophilic pneumonias and in allergic bronchopulmonary aspergillosis (ABPA) and often precedes the diagnosis of these 2 conditions.

Other symptoms of fever, myalgia, fatigue, weight loss, poor appetite, and night sweats may accompany the acute or chronic eosinophilic pneumonias. When abnormalities of the liver are detected, or if arthralgia, skin changes, pericardial effusion, or peripheral neuropathy accompany the disease presentation, a diagnosis of eosinophilic GPA (formerly known as the Churg-Strauss syndrome) or the hypereosinophilic syndrome should be aggressively investigated.

**Chest Imaging**

The chest radiograph is one of the most helpful tests in evaluating the child with dyspnea. The characteristic feature of fluffy alveolar infiltrates in the peripheral lung field is classic (Fig. 399-5). The images may be easily recognizable by astute clinicians who have identified the etiology of the disease without eosinophil counts or BAL.

HRCT is the best advanced imaging modality for eosinophilic lung disease. Spontaneous migration of lung opacities is commonly seen in the chronic pneumonias. Most often HRCT shows simultaneous evidence of bilateral alveolar infiltrates with both confluent consolidations and ground glass appearance. The most prominent areas of abnormality are visualized in the upper lobes and subpleural regions. Specific diseases have unique findings, such as proximal bronchiectasis in ABPA and pleural effusion in acute eosinophilic pneumonia. HRCT is most sensitive in identifying the correct etiology of disease when chest radiographic findings are nonspecific.

**LÖFFLER SYNDROME**

The transient pulmonary infiltrates with eosinophilia syndrome that is most often seen in children (formerly known as LöFFler syndrome) is characterized by migrating pulmonary infiltrates with peripheral blood eosinophilia caused by the helminthic infections. *A. lumbricoides* or roundworm is the most common parasite causing this disease in the United States. When a fertilized egg is ingested from contaminated food, it becomes a larval worm that can penetrate the duodenum of the small intestine and migrate in the circulation to the liver, heart, and lungs. In the pulmonary venous circulation, the larvae can break through the interstitial space to the alveoli. The juvenile larva may subsequently migrate to the trachea where they are coughed up and swallowed. The cycle may then recur with subsequent absorption of eggs that are produced in the intestinal tract. Other nematodes cannot mature in the intestinal tract so their disease is limited to a single passage into the lungs.

**Visceral larva migrans** from multiple nematodes may cause this disease. The most common cause of these includes the dog roundworm, *Toxocara canis*, while *Toxocara cati*, *Strongyloides stercoralis*, *Baylisascaris procyonis*, and *Loagochilascaris minor* can all produce visceral larva migrans. Outside the United States, the common lung fluke, *Paragonimus westermani*, may cause a similar pulmonary disease in older children and adolescents. Western Africa, Central and South America, and the Far East are regions that paragonimiasis may be found, especially in those who eat raw crabs or crawfish. Many other parasites may have a transient pulmonary syndrome, but their diseases are most commonly manifested in other organs.

The pulmonary syndrome is classic with cough, dyspnea, migratory peripheral pulmonary infiltrates, and blood eosinophilia that is self-limited. Young children most often have a history of pica and eating dirt that is contaminated with the eggs. Because the larva can migrate to other organs as well as multiply in the intestinal and biliary tract, symptoms of abdominal pain, vomiting, rarely obstruction, cholecystitis, and pancreatitis may be found. Diagnosis is frequently made by examination of the stool where the eggs may be detected microscopically. Treatment is aimed at the intestinal disease and not the pulmonary disease per se. It is possible that antihelminthic treatment of other organ disease during the pulmonary phase of the disease will increase the inflammatory response in the lung and may require corticosteroid therapy.

### Table 399-8

<table>
<thead>
<tr>
<th>Key Elements in the Medical History and Physical Exam to Raise Clinical Suspicion for Diagnostic Testing to Confirm Eosinophilic Lung Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history and examination</td>
</tr>
<tr>
<td>• Drug exposure (especially antibiotics, NSAIDs, antiepileptics,</td>
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<tr>
<td>antiulotriene modifiers in EGPA)</td>
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<tr>
<td>• Environmental inhalation exposures to dust or inhaled chemicals</td>
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<tr>
<td>• New onset of smoking cigarettes</td>
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<tr>
<td>• Travel or immigration status from areas endemic with various parasites or coccidiomycosis</td>
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<tr>
<td>• Asthma (may be severe or poorly controlled with ABPA, CSS, or is relatively new in onset with IAEP)</td>
</tr>
<tr>
<td>• ABPA concurrent in 7-10% of patients with cystic fibrosis</td>
</tr>
<tr>
<td>• Extrapulmonary symptoms suggestive of vasculitis, neuropathy, heart failure, or neoplasm</td>
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<tr>
<td>• Rash (creeping eruption in visceral larval migrans disease or ulceration in EGPA)</td>
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<tr>
<td>Diagnostic imaging and testing</td>
</tr>
<tr>
<td>• Radiography helpful in AEP, CEP, and ABPA</td>
</tr>
<tr>
<td>• Radiography not diagnostic in EGPA or drug-induced eosinophilic disease of the lung</td>
</tr>
<tr>
<td>• Simple chest radiography findings</td>
</tr>
<tr>
<td>• Nonlobar infiltrate</td>
</tr>
<tr>
<td>• Classic description as mirror image of pulmonary edema with peripheral infiltrates</td>
</tr>
<tr>
<td>• Bilateral pleural effusion in AEP</td>
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<tr>
<td>• Central bronchiectasis in ABPA</td>
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<tr>
<td>• High-resolution computerized tomography of the chest</td>
</tr>
<tr>
<td>• Middle and upper lobe nonlobar infiltrates with areas of ground-gllass appearance</td>
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<tr>
<td>• Mucous plugging in ABPA</td>
</tr>
<tr>
<td>• Central bronchiectasis in ABPA (confused with cystic fibrosis)</td>
</tr>
<tr>
<td>• Blood eosinophil count</td>
</tr>
<tr>
<td>• Elevated in many eosinophilic lung diseases</td>
</tr>
<tr>
<td>• Magnitude of eosinophil blood count does not distinguish different pulmonary diseases</td>
</tr>
<tr>
<td>• Usually not elevated in AEP (eosinophilic disease compartmentalized to lungs)</td>
</tr>
<tr>
<td>• May occasionally not be elevated in CEP or after use of corticosteroids</td>
</tr>
<tr>
<td>• Total serum IgE elevated in ABPA but not always in patients with cystic fibrosis with ABPA</td>
</tr>
<tr>
<td>• Serology for helminthic infections or parasites may be diagnostic but are usually not available acutely</td>
</tr>
<tr>
<td>• P-ANCA (MPO ANCA) is positive in 40-70% of EGPA (CSS)</td>
</tr>
<tr>
<td>• BAL eosinophil percentage</td>
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<tr>
<td>• ≥25% eosinophils diagnostic in AEP</td>
</tr>
<tr>
<td>• ≥40% eosinophils diagnostic in CEP or tropical pulmonary eosinophilia</td>
</tr>
<tr>
<td>• Eosinophil percentages below these criteria may require lung biopsy</td>
</tr>
<tr>
<td>• &lt;25% eosinophils seen in connective tissue disease, sarcoid, drug-induced disease, histiocytosis X of pulmonary Langerhans cells, and interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td>• Lung biopsy</td>
</tr>
<tr>
<td>• Open lung biopsy or video-assisted thoracoscopic surgery when BAL nondiagnostic</td>
</tr>
<tr>
<td>• Transbronchial biopsy is usually insufficient with peripheral infiltrative disease</td>
</tr>
<tr>
<td>• Histology with alveolar and interstitial infiltrates of eosinophils, non-necrotizing non-granulomatous vasculitis, multinucleated giant cells without granuloma</td>
</tr>
<tr>
<td>• EGPA shows eosinophil rich small to medium vessel, necrotizing, granulomatous vasculitis</td>
</tr>
</tbody>
</table>

ABPA, allergic bronchopulmonary aspergillosis; AEP, acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; CEP, chronic eosinophilic pneumonia; CSS, Churg-Strauss syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; IAEP, idiopathic acute eosinophilic pneumonia; MPO ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; NSAID, nonsteroidal anti-inflammatory drug; P-ANCA, perinuclear antineutrophil cytoplasmic antibody.
Chapter 399 – Immune and Inflammatory Lung Disease

ACUTE EOSINOPHILIC PNEUMONIA

A unique and dramatic presentation of the eosinophilic pneumonias is AEP. AEP mimics infectious pneumonia or acute respiratory distress syndrome with its rapid onset and marked hypoxemia. In pediatrics, this disease most frequently occurs in the teenage population. Overall, young adults most commonly contract this idiopathic disease. Essentially all patients present within 7 days of symptom onset with dyspnea, fever, and cough, and more than 50% have chest pain. Myalgia and abdominal pain also frequently accompany this disease. Rarely, patients have presented up to 4-5 wks after onset of symptoms. Physical exam demonstrates tachypnea, tachycardia, and crackles in the lung fields on physical exam. Many patients rapidly deteriorate and require mechanical ventilation.

There is an absence of circulating eosinophilia, which contrasts the dramatic number of eosinophils seen in the BAL representing at least 25% of the inflammatory cells (often 40-55%) (Fig. 399-6). This feature helps distinguish it from the chronic pulmonary disease of eosinophilic origin.

Although this disease has been labeled as idiopathic, there have been identifiable exposures (e.g., 1,1,1-trichloroethane or Scotchgard). Numerous reports link onset of smoking tobacco, change in smoking frequency, initiation of smoking in young male adolescents or adults, and even massive secondary smoke exposure as critical associations with onset of AEP. World Trade Center dust is associated with development of AEP. A single smoke challenge study is associated with recurrence. Some medications are also linked to the onset of AEP. The most complete and current resource for medications linked to pulmonary disease is ‘The Drug-Induced Respiratory Disease Website’ (http://www.pneumotox.com). When AEP is identified in a patient, the pediatrician’s role in educating the patient and family about the link to smoking exposure and risk of AEP upon reexposure is warranted.

In addition to smoke exposure, AEP has been reported after smoking cocaine within hours to days after exposure. Whether this is a unique eosinophilic response to cocaine that represents one manifestation of “crack lung” or is a separate disease is unknown. “Crack lung” refers to diffuse alveolitis with pulmonary hemorrhage from an unknown mechanism that occurs within 48 hr of cocaine smoke inhalation.

Lung function has not been measured frequently in the disease because the patients have proceeded rapidly to the ICU and need for mechanical ventilation. When measured, a restrictive pattern of lung disease and reduced diffusion capacity is the usual finding arterial blood gases will show a significant increase in the alveolar–arterial gradient (see Chapter 373).

The criteria for diagnosis include the acute onset of disease, bilateral pulmonary infiltrates, reduced oxygen saturation or \( \text{PaO}_2 \leq 60 \text{ mm Hg} \), BAL of \( \geq 25\% \), and absence of a determined cause of eosinophilia. The recent onset of tobacco exposure, dust, or chemical inhalation is supporting factors in confirming a diagnosis.

Treatment has uniformly been the use of a corticosteroid (e.g., methylprednisolone 1-2 \( \text{mg/kg/day} \)) either intravenously or orally for 2-4 wks. A minimum or maximum treatment time has not been determined, but relapses or persistent symptoms are uncommon. Rare fatalities have been reported. Complete recovery has been seen in days with resolution of pleural effusions within the 4 wk treatment time. Most important, relapse has been rare, which sharply contrasts the idiopathic chronic eosinophilic pneumonias. Follow-up testing of pulmonary functions are usually normal which supports the contention that lung parenchyma heals without evidence of compromise or fibrosis.

CHRONIC EOSINOPHILIC PNEUMONIA

Chronic eosinophilic pneumonia is another idiopathic pulmonary condition without a known exposure to toxin, dust, or chemical inhalation. Eosinophils infiltrate the lung parenchyma resulting in dyspnea, cough, fever, and weight loss. It is primarily a problem for adults, with a female predominance (2:1 female:male ratio) usually in patients who are nonsmokers. Chest examination reveals tachypnea, crackles, and occasional wheezing as preceding asthma is a common finding. The classic finding on chest x-ray of the “radiographic negative of

Figure 399-5 Acute eosinophilic pneumonia demonstrating the mirror image (A) pulmonary edema with a right pleural effusion on admission and (B) complete clearing upon discharge from the hospital after corticosteroid usage.

Figure 399-6 Light microscopy of eosinophils in bronchoalveolar lavage fluid.
pulmonary edema” is found in these patients: central clear lung fields but fluffy, patchy peripheral infiltrates of the lung parenchyma.

When compared to AEP, the onset of disease is indolent and subtle but the accompanying fever and weight loss may lead the clinician to a concern for an underlying malignancy prior to chest radiograph and laboratory investigation. Peripheral blood eosinophilia is commonly as high as 5000/mm³ or greater, accompanied by BAL eosinophilia >40% on the differential count. The peripheral eosinophils sharply contrasts the lack of eosinophils seen in the blood in AEP. HRCT scan contrasts the AEP with pleural effusion as a rare finding, as well as rare cavitation.

In contrast to AEP, pulmonary function testing shows a mixed obstructive and restrictive pattern as a result of asthma occurring concurrently with pneumonia.

Inflammatory markers associated with migration and activation of eosinophils are predictably found in BAL and the urine. These include the T-lymphocyte type 2 cytokines of IL-4, IL-5, IL-6, IL-10, IL-13, and eosinophils are predictably found in BAL and the urine. These include IL-18. However, T-lymphocyte type 1 cytokines of IL-2 and IL-12 are the T-lymphocyte type 2 cytokines of IL-4, IL-5, IL-6, IL-10, IL-13, and IL-18. However, T-lymphocyte type 1 cytokines of IL-2 and IL-12 are also present with many of the potent eosinophilic chemooattractants such as CCL5 (RANTES [regulated upon activation, normal T cell expressed and secreted]) and CCL11 (eotaxin-1). Toxic granule proteins of major basic protein, eosinophil-derived neurotoxin, and eosinophil cationic protein are frequently present. Unfortunately, these important molecules help confirm the eosinophilic nature of the disease, but their presence adds no additional sensitivity or specificity over the presence of eosinophils on BAL.

Treatment is similar to most eosinophilic lung syndromes where corticosteroids (oral) are the mainstay of treatment. The minimum dose of steroid needed to induce remission is not known, but most clinicians recommend prednisone (or equivalent) at 0.5 mg/kg/day for 2 wks. The dose is reduced to half (0.025 mg/kg/day) for an additional 2 wks if symptoms have abated. The remaining dose of steroid may need to be weaned over 6 mo. Symptoms and pulmonary infiltrates rapidly disappear after initiation of this treatment but frequently recur with tapering of the steroid. Asthma concurrently in patients with chronic eosinophilic pneumonia identifies a phenotype of the disease that appears to have lower relapse risk yet up to 50% of all identified patients with chronic eosinophilic pneumonia relapse during or after corticosteroid taper.

Many believe that this disease is a precursor to the development of eosinophilic granulomatosis with polyangiitis (EGPA) or the Churg-Strauss syndrome. The utility of inhaled corticosteroids in chronic eosinophilic pneumonia is unknown but is warranted for the persistent asthma phenotype of disease. A subset of patients develop permanent lower airway obstruction without reversibility, which requires patients with this disease to have close follow-up and monitoring of pulmonary function tests routinely.

**EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (THE CHURG-STRAUSS SYNDROME)**

The EGPA syndrome is a systemic disease involving multiple organs but most prominently the lung. Patients present with difficult to control asthma, allergic rhinitis, and peripheral eosinophilia (>10% or >1,500 cells/µL) in the blood. Evidence of vasculitis on clinical grounds must be present in at least 2 organs. The polyangiitis appears later in the disease process with asthma being the precursor symptom in more than 90% of the cases reported. EGPA affects multiple organs including the skin, heart, gastrointestinal tract, kidneys, and central nervous system. Rhinitis is present in 75% of the patients but is not specific. Symptom complexes of fever, weight loss, fatigue, arthralgia, and myalgia may be seen in approximately two-thirds of patients. Cardiac and renal involvement is insidious in onset and should be screened for. It is the multiple organ involvement that results in the morbidity and mortality of this disease. The typical progression of the disease is in 3 phases: rhinitis and asthma first, tissue eosinophilia second, and, finally, systemic vasculitis.

The pathogenesis of EGPA is still unknown but several factors are suspected to contribute to the development of the disease. The possible link between leukotriene-receptor antagonists (zafirlukast, montelukast, or pranlukast) is controversial but still considered possible. It is suspected that use of this class of adjunctive medications in severe asthma allows for the reduction in use of corticosteroid leading to the full blown (unmasking) manifestation of EGPA. Isolated use of leukotriene-receptor antagonists may induce disease, lead to remission with cessation of leukotriene-receptor antagonists, and cause recurrence of EGPA upon reintroduction of this class of medications. Many refrain from use of leukotriene-receptor antagonists when the EGPA syndrome has been diagnosed.

Clinical and laboratory finding are able to pinpoint the diagnosis with high specificity (99.7%) and sensitivity (85%) when 4 of 6 criteria are met (asthma, eosinophilia >10%, mononeuropathy or polynuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormalities, and biopsy findings of extravascular eosinophil infiltrates). In contrast to GPA, the rhinitis is not destructive and nasal septal perforation does not occur in EGPA.

Radiography of the chest by plain radiography or HRCT demonstrates the migratory, peripheral predominant opacities with ground-glass appearance to full consolidation. Bronchiectasis and bronchial wall thickening are reported. Pleural effusion should raise suspicion for the presence of heart failure from cardiomyopathy.

Laboratory findings include striking eosinophilia with values generally between 5,000 and 20,000/mm³ at the time of diagnosis. These counts often parallel the vasculitis activity that is found. The BAL shows striking eosinophilia with differential counts of >60%. Other organ system levels reflect activity of eosinophils and are not specific for the EGPA diagnosis.

ANCAs are present in the EGPA syndrome. The perinuclear-ANCA targeting myeloperoxidase are specifically found in EGPA in approximately 40% of the patients; the absence of myeloperoxidase-ANCA does not exclude the diagnosis. Those patients with eosinophilic pneumonia, fever, and cardiac involvement are less likely to have myeloperoxidase-ANCA detected. Those with peripheral neuropathy, renal glomerular disease, and skin purpura usually have detectable myeloperoxidase-ANCAs.

Pulmonary function tests while on bronchodilators and inhaled corticosteroids for asthma show an obstructive pattern. The pulmonary obstruction is responsive to oral corticosteroid use but often has mild persistence of obstruction.

Treatment of EGPA with systemic oral corticosteroid remains the mainstay of therapy at a starting dose of 1 mg/kg/day for 4 wks. This therapy is often required for up to 12 mo or longer with a steady taper in dosage over that time. EGPA resistant to corticosteroid has responded to cyclophosphamide, IFN-α, cyclosporine, intravenous immunoglobulin, and plasmapheresis. The use of anti–IL-5 (mepolizumab) has been encouraging and may be used as a steroid-sparing agent in the future.

**ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS**

ABPA is a complex mixed immunologic hypersensitivity reaction in the lungs and bronchi in response to exposure and colonization of Aspergillus species (usually Aspergillus fumigatus; see Chapter 327.1). This disease almost exclusively occurs in patients with preexisting asthma and up to 15% of patients with cystic fibrosis (see Chapter 402). The quantity of Aspergillus exposure does not correlate to the severity of disease.

The clinical pattern of disease (Table 399-9) is remarkably similar with a clinical presentation of difficult-to-treat asthma, periods of acute obstructive lung disease with bronchial mucous plugs, elevated total IgE antibody, elevated specific IgE and IgG anti-Aspergillus antibodies, skin prick test reactions to Aspergillus species, precipitating antibody to Aspergillus species, as well as proximal bronchiectasis. Other clinical manifestations include dyspnea, cough, shortness of breath, production of brown mucous plugs frequently characterized as “rubber” plugs, and peripheral eosinophilia, as well as pulmonary eosinophilia with infiltration of the parenchyma. The use of systemic corticosteroid may lower the total IgE antibody levels such that
a diagnosis may be in question when the first tests are performed at that time.

ABPA should be considered in patients with cystic fibrosis when clinical deterioration occurs without evidence of an identifiable cause. Symptoms heralding such deterioration include increasing cough, wheezing, loss of exercise tolerance, worsening exercise-induced asthma, reduction of pulmonary function, or increased sputum production without another discernible reason. Clinical findings of elevated total IgE antibody, anti-Aspergillus IgE, precipitating antibodies to Aspergillus fumigatus, and/or new abnormalities on chest radiography that fail to clear with antibiotics should alert the clinician to the possibility of ABPA.

When evaluating a child with asthma symptoms, the clinician must distinguish asthma from ABPA. If the diagnosis is suspected, skin prick test for evidence of IgE-specific antibody directed against A. fumigatus is essential. Intradermal skin testing when the skin prick test is negative, although not routinely performed because of poor specificity, may be performed. The absence of a positive skin prick test and intradermal test to A. fumigatus virtually excludes the diagnosis of ABPA. The prevalence of ABPA in patients with an existing diagnosis of asthma and an abnormal immediate skin prick test response to A. fumigatus has been evaluated. Between 2% and 32% of patients with asthma with concurrent skin prick test–positive reactions to Aspergillus have evidence of ABPA.

It is uncommon for the patient with cystic fibrosis to develop ABPA before the age of 6 yr. When the total IgE antibody in patients with cystic fibrosis exceed 500 IU/mL (1,200 ng/mL), a strong clinical suspicion of ABPA is necessary.

ABPA pathology has characteristic findings of mucoid bronchi impaction, eosinophilic pneumonia, and bronchocentric granulomas in addition to the typical histologic features of asthma. Septated hyphae are often found in the mucus-filled bronchial tree. However, the fungi do not invade the mucosa in this unique disease. Aspergillus may be cultured from sputum in more than 60% of ABPA patients. Interestingly, hyphae may not always be seen on microscopy.

Staging of the disease (Table 399-10) represents distinct phases of the disease but do not necessarily progress in sequence from stage 1 to stage 5. Staging of ABPA is important for treatment considerations. In many hypersensitivity diseases where IgE antibody contributes to the pathogenesis (e.g., asthma), total IgE is often used for screening for an atopic state, but is not a test that helps the clinician with serial measures. In sharp contrast, the measurement of IgE during acute exacerbations, remission, and recurrent ABPA disease is helpful in identifying the activity of disease and may herald the recurrence. During stage 1 disease, the level of IgE antibody is often very high. During stage 2 remission, a fall in the levels may be as much as 35% or more. Recurrence of activity may result in a marked rise of total IgE with a doubling of the baseline level seen during remission. During the use of glucocorticoid therapy, monthly or bimonthly levels of IgE are followed serially to assist the clinician in tapering therapy. Because exacerbations of ABPA are asymptomatic to the patient in approximately 25% of the recurrences, serial IgE accompanied by chest radiography are helpful to the clinician to guide therapy.

**Radiography**

Plain chest X-ray shows evidence of infiltrates especially in the upper lobes and the classic findings of bronchiectasis (Fig. 399-7). The use of HRCT demonstrates central bronchiectasis in the central regions of the lung (Fig. 399-8). HRCT may add value in the patient with a positive skin prick test and normal chest radiograph in detecting characteristic abnormalities of ABPA.

**Treatment**

The mainstay of therapy for ABPA has been systemic glucocorticoids with adjunct therapy with antifungal medications and anti-IgE therapy with omalizumab. Exacerbations in stages 1 and 3 are treated for 14 days with 0.5-1 mg/kg of glucocorticoid followed by every-other-day usage and tapering over 3 mo or as long as 6 mo. Stage 2 remission phase and stage 5 where fibrosis has occurred do not require glucocorticoid therapy. Stage 4 denotes a state where glucocorticoid weaning has not been successful and continued long-term therapy is required. Antifungal therapy with a 16 wk course of itraconazole improves the response rate during exacerbations that allowed reduction of glucocorticoid dosage by 50% accompanied by a reduction of total serum IgE of 25% or more. The proposed mechanisms of action have been to either reduce the antigen load driving the immune response or possibly raising the serum levels of corticosteroid by slowing the metabolism.

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**Table 399-9**  The Classification of the Eosinophilic Lung Diseases

<table>
<thead>
<tr>
<th>IDIOPATHIC</th>
<th>KNOWN ETIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute eosinophilic pneumonia</td>
<td>Drug-induced eosinophilic pneumonia</td>
</tr>
<tr>
<td>Chronic eosinophilic pneumonia</td>
<td>Infectious causes</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangitis</td>
<td>Astasiais (Löffler syndrome)*</td>
</tr>
<tr>
<td>Hypereosinophilic syndromes</td>
<td>Toxocara (canis or cat)</td>
</tr>
<tr>
<td>Myeloproliferative variant</td>
<td>Filarial (tropical filarial eosinophilic pneumonia)</td>
</tr>
<tr>
<td>Lymphocytic variant</td>
<td>Strongyloides stercoralis</td>
</tr>
<tr>
<td></td>
<td>Allergic bronchopulmonary aspergilosis</td>
</tr>
<tr>
<td></td>
<td>Toxic</td>
</tr>
<tr>
<td></td>
<td>L-Tryptophan (eosinophilic myalgia syndrome)</td>
</tr>
<tr>
<td></td>
<td>Toxic oil syndrome</td>
</tr>
<tr>
<td></td>
<td>Illicit drug use (cocaïne, heroin, cannabis)</td>
</tr>
</tbody>
</table>

*Note: Löffler eosinophilic pneumonia has transient symptoms and is often classified as neither an acute or chronic eosinophilic pneumonia.

**Table 399-10**  Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis

<table>
<thead>
<tr>
<th>Staging of allergic bronchopulmonary aspergillosis</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Upper and middle lobe infiltration</td>
<td>High IgE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>No infiltrate off steroids &gt;6 mo</td>
<td>Normal to high IgE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation</td>
<td>Upper and middle lobe in filtrations</td>
<td>High IgE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSD asthma</td>
<td>Minimal infiltrate</td>
<td>Normal to high IgE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End stage</td>
<td>Fibrosis and/or bullae</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The criteria required for diagnosis of ABPA with central bronchiectasis. †The first 4 criteria are required for a diagnosis of seropositive ABPA. CSD, corticosteroid dependent.
The hypereosinophilic syndrome (HES) is a descriptive name of a group of disorders that are characterized by the persistent overproduction of eosinophils accompanied by eosinophil infiltration in multiple organs with end-organ damage from mediator release. The term HES should only be used when there is eosinophilia with end-organ damage from the eosinophils and not from another cause. The discovery of underlying genetic, biochemical, or neoplastic reasons for HES has led to the classification of primary, secondary, and idiopathic HES (Table 399-11). Specific syndromes such as EGPA (Churg-Strauss) have eosinophilia but the contribution of eosinophils to the organ damage is incompletely understood.

Some variants of HES have genetic mutations in tyrosine kinase receptor platelet-derived growth factor receptor-α (PDGFRα); males are almost exclusively affected. Otherwise, HES appears to be distributed equally among females and males.

Hypereosinophilia is defined as an absolute eosinophil number in the blood that exceeds \(1.5 \times 10^9\) eosinophils on 2 separate occasions.

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Hypereosinophilia is defined as an absolute eosinophil number in the blood that exceeds \(1.5 \times 10^9\) eosinophils on 2 separate occasions.
Hypereosinophilic Syndrome Variants

Clinical manifestations of the HES include organ involvement of the heart (5%), gastrointestinal (14%), skin (37%), and pulmonary (25%-63%). The HES is complicated by thrombosis and/or neurologic disease in many patients, although the exact prevalence of this problem is incompletely categorized. Peripheral neuropathy, encephalopathy, transverse sinus thrombosis, or cerebral emboli are the most common neurologic complications. The exact mechanism of the manifestations is unclear especially in major artery thrombosis such as the femoral artery.

The most frequent pulmonary symptoms include cough and dyspnea. Many patients have obstructive lung disease with clinical wheezing. Evidence of pulmonary fibrosis and pulmonary emboli are seen with regularity. Because biopsy shows eosinophilic infiltrates similar to other pulmonary eosinophilic diseases of the lung, it is the constellation of other organ involvement or thromboembolic phenomena and other organs that must lead the clinician to a high index of suspicion for the HES.

Laboratory evaluation should include evaluation of liver enzymes, kidney function tests, creatine kinase, and troponin. The extent of cardiac involvement should be evaluated by electrocardiogram and echocardiogram. Some unique biomarkers may be tested when evaluating the myeloproliferative and T-lymphocyte HES diagnoses. Vitamin B₁₂, and serum tryptase may be elevated, especially the latter, when the myeloproliferative disease is accompanied by mastocytosis. These 2 biomarkers are most frequently elevated when the mutation is present or fusion in the FIP1L1/PDGFRα sites.

Because of the extensive pulmonary disease that is seen in the HES, pulmonary function tests should be performed at diagnosis when possible to include spirometry and lung volumes. Dead space ventilation may be significantly elevated in the patients with pulmonary emboli. Pulse oximeter may be very helpful in the evaluation as well.

Chest radiography and CT are very helpful in the evaluation. Spiral chest CT should also be performed when pulmonary emboli are being considered. In one series of patients, nearly half of the patients with HES had evidence of pulmonary abnormalities including ground-glass appearing infiltrates, pulmonary emboli, mediastinal lymphadenopathy, and/or pleural effusion.

Treatment of HES depends on the type of variant (myeloproliferative, lymphocytic forms, undefined, associated with systemic diseases such as EGPA or familial). Rarely, some patients present with marked eosinophilia where the total count exceeds 100,000 cells/µL and vascular insufficiency symptoms. Prednisone at 15 mg/kg is indicated to acutely reduce the eosinophil count, after diagnostic tests are performed, when safe. If the patient is unstable, the glucocorticoid should be administered to prevent progression of symptoms. Other acute therapies aimed at reduction of eosinophil counts include vincristine, imatinib mesylate, or even leukapheresis.

When eosinophil counts are not as dramatically elevated, therapy begins with glucocorticoids at 1 mg/kg for patients who do not have the FIP1L1/PDGFRα mutation. Patients with this mutation are resistant to glucocorticoids and initial treatment should begin with imatinib, a tyrosine kinase inhibitor. Because this genetic test is often not readily available, surrogate markers for the presence of this mutation are vitamin B₁₂ levels >2000 pg/mL or serum tryptase >11.5 ng/mL. It denotes the presence of resistant disease that should initially be treated with imatinib. The goal of therapy is to reduce and maintain eosinophil counts below 1.5 × 10⁶ at the lowest dose of prednisone possible to reduce or avoid corticosteroid side effects. If corticosteroid doses can't be lowered below 10 mg/day, then imatinib can be added as combination therapy in order to spare the dose of steroid. Caution must be used in the presence of cardiac disease as introduction of imatinib has precipitated left ventricular failure.

Additional or alternative adjunct therapies that have shown promise include hydroxyurea, interferon α, anti–IL-5 monoclonal antibody therapy; and a monoclonal antibody directed against CD52. Failure of

Table 399-11  Hypereosinophilic Syndrome Variants

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloproliferative</td>
<td>Nonclonal&lt;br&gt;Clonal FIP1L1/PDGFRα-positive chronic eosinophilic leukemia</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>Nonclonal T cells&lt;br&gt;Clonal T-cell expansion with T-cell activation</td>
</tr>
<tr>
<td>Overlap</td>
<td>Organ restricted</td>
</tr>
<tr>
<td>Familial</td>
<td>Family history of eosinophilia without known cause</td>
</tr>
<tr>
<td>Associated</td>
<td>Eosinophilia in chronic disease like inflammatory bowel disease or EGPA</td>
</tr>
<tr>
<td></td>
<td>(Churg-Strauss syndrome)</td>
</tr>
<tr>
<td>Undefined</td>
<td>Asymptomatic&lt;br&gt;Cyclic angioedema with eosinophilia&lt;br&gt;Clonal T-cell expansion</td>
</tr>
<tr>
<td></td>
<td>Symptomatic without myeloproliferation or lymphocytic form</td>
</tr>
</tbody>
</table>

EGPA, eosinophilic granulomatosis with polyangiitis; PDGFRα, platelet-derived growth factor receptor-α.
the above modalities may signal a need for hematopoietic stem cell transplantation. This therapy has been successful in some patients.

Bibliography is available at Expert Consult.

399.5 Interstitial Lung Disease  
**Kevin J. Kelly**

ILD in children is caused by a large group of uncommon, heterogeneous, familial, or sporadic diseases that involve the pulmonary parenchyma and cause significant impairment of gas exchange. The ILDs in pediatrics are uncommonly caused by infectious processes and specific immunologic processes when compared to adults. The one exception to this is Goodpasture disease with classic anti-basement membrane antibodies. Despite wide variations in cause, these disorders are classified together because of the similar clinical, physiologic, radiographic, and pathologic processes involving disruption of alveolar interstitium and airways. A survey of all German pediatric hospitals found a rate of occurrence of pediatric ILD of 1.3 children/million population. The pathophysiology is believed to be more complex than that of adult disease because pulmonary injury occurs during the process of lung growth and differentiation. In ILD, the initial injury causes damage to the alveolar epithelium and capillary endothelium. Abnormal healing of injured tissue may be more prominent than inflammation in the initial stages of the development of chronic ILD. Some familial cases, especially in the surfactant dysfunction disorders, involve a specific genetic mutation.

**CLASSIFICATION AND PATHOLOGY**

Classification of ILD in children is not standardized. It is helpful for the clinician to separate diseases into ILD on the basis of age, disorders of known and unknown etiology, and diseases related to systemic disorders (Table 399-12). A diffuse developmental disorder of the lung is likely the result of a primary aberration in lung and/or pulmonary vascular development. Growth abnormalities reflecting deficient development of alveoli are largely secondary to impaired prenatal or postnatal alveolarization from restriction of fetal thoracic space, limitation of pulmonary blood supply, or chronic lung disease of prematurity (e.g., bronchopulmonary dysplasia) (see Chapter 101). Abnormal alveolar growth may also be associated with a variety of chromosomal abnormalities such as trisomy 21. In neuroendocrine cell hyperplasia of infancy/persistent tachypnea of infancy, a distinct entity limited to infants and young children, the pathologic findings include hyperplasia of neuroendocrine cells within the bronchioles while the pulmonary histologic background is nearly normal. Pulmonary interstitial glycogenosis is characterized by diffuse accumulation of mesenchymal cells in the alveolar interstitium with accumulation of monoparticulate glycogen in the interstitial cell cytoplasm that is confirmed by ultrastructural examination.

Disorders associated with surfactant metabolism dysfunction explain many of formerly idiopathic pediatric ILDs. The more-severe surfactant dysfunctions, such as surfactant protein-B mutations, usually manifest as respiratory failure in neonate. Congenital pulmonary alveolar proteinosis is more typical of ABCA3 mutations, and chronic pneumonitis of infancy is predominant histologic pattern seen in surfactant protein-C mutations. Age-related but overlapping surfactant disorders in addition to pulmonary alveolar proteinosis and chronic pneumonitis of infancy also include desquamative interstitial pneumonia in infants; older children and adolescents more often manifest nonspecific interstitial pneumonia or usual interstitial pneumonia. ABCA3 mutations may produce pulmonary alveolar proteinosis, desquamative interstitial pneumonia, or nonspecific interstitial pneumonia; surfactant protein-C deficiency may also produce chronic pneumonitis of infancy in older children.

Diffuse ILD can occur without a known immunodeficiency or systemic disorder, but it can also be seen as a pulmonary manifestation of other systemic disease processes, such as collagen vascular disorders and sarcoidosis.

### Table 399-12 | The Pediatric Interstitial Lung Diseases

#### AGE-RELATED ILDS IN INFANCY AND EARLY CHILDHOOD

- Diffuse developmental disorders
  - Acinar dysplasia
  - Congenital alveolar dysplasia
  - Alveolar capillary dysplasia with misalignment of pulmonary veins (some due to FOXF1 mutation)
  - Growth abnormalities reflecting deficient alveolarization
  - Pulmonary hypoplasia
  - Chronic neonatal lung disease
  - Chromosomal disorders
  - Congenital heart disease
  - Neuroendocrine cell hyperplasia of infancy
  - Pulmonary interstitial glycogenosis (infantile cellular interstitial pneumonia)
  - Surfactant dysfunction disorders (pulmonary alveolar proteinosis)
  - Surfactant protein-B mutation
  - Surfactant protein-C mutation
  - ABCA3 mutation
  - Granulocyte-macrophage colony-stimulating factor receptor (CSF2RA) mutation

#### ILD DISORDERS WITH KNOWN ASSOCIATIONS

Infectious/postinfectious processes
- Adenovirus infections
- Influenza viruses
- Chlamydia pneumoniae
- Mycoplasma pneumoniae
- Environmental agents
- Hypersensitivity pneumonitis
- Toxic inhalation
- Aspiration syndromes

#### PULMONARY DISEASES ASSOCIATED WITH PRIMARY AND SECONDARY IMMUNE DEFICIENCY

Opportunistic infections
- Granulomatous lymphocytic ILD associated with common variable immunodeficiency syndrome
- Lymphoid intestinal pneumonia (HIV infection)
- Therapeutic interventions: chemotherapy, radiation, transplantation, and rejection

Idiopathic ILDs
- Usual interstitial pneumonia
- Desquamative interstitial pneumonia
- Lymphocytic interstitial pneumonitis and related disorders
- Nonspecific interstitial pneumonitis (cellular/fibrotic)
- Eosinophilic pneumonia
- Bronchiolitis obliterans syndrome
- Pulmonary hemosiderosis and acute idiopathic pulmonary hemorrhage of infancy
- Pulmonary alveolar proteinosis
- Pulmonary vascular disorders
- Pulmonary lymphatic disorders
- Pulmonary microlithiasis
- Persistent tachypnea of infancy
- Brain-thyroid-lung syndrome

#### SYSTEMIC DISORDERS WITH PULMONARY MANIFESTATIONS

Goodpasture disease
- Gaucher disease and other storage diseases
- Malignant infiltrates
- Hemophagocytic lymphohistiocytosis
- Langerhans cell histiocytosis
- Sarcoidosis
- Systemic sclerosis
- Polymyositis/dermatomyositis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Lymphangioliomyomatosis
- Pulmonary hemangiomas
- Neurocutaneous syndromes
- Hermansky-Pudlak syndrome

Bibliography
Persistent pulmonary symptoms can occur after respiratory infections caused by adenoviruses, influenza viruses, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. Aspiration is a frequent cause of chronic lung disease in childhood. Children with developmental delay or neuromuscular weakness are at an increased risk for aspiration of food, saliva, or foreign matter secondary to swallowing dysfunction and/or gastroesophageal reflux. An undiagnosed tracheoesophageal fistula can also result in pulmonary complications related to aspiration of gastric contents and interstitial pneumonia.

Children experiencing an exaggerated immunologic response to organic dust, molds, or bird antigens may demonstrate hypersensitivity pneumonitis. Children with malignancies may have ILD related to the primary malignancy or an opportunistic infection or secondary to chemotherapy or radiation treatment.

**CLINICAL MANIFESTATIONS**
A detailed history is needed to assess the severity of symptoms and the possibility of an underlying systemic disease in a patient with suspected ILD. Identification of precipitating factors, such as exposure to molds or birds and a severe lower respiratory infection, is important in establishing the diagnosis and instituting avoidance measures. A positive family history, especially in an affected infant, is suggestive of a genetic or familial disease, such as a surfactant dysfunction. Tachypnea, dyspnea, cough, and failure to thrive are commonly present. The majority of patients develop hypoxia and hypercarbia, usually a late and ominous complication. Symptoms are usually insidious and occur in a continuous, not episodic, pattern. Tachypnea, crackles on auscultation, and retractions are noted on physical examination in the majority of children with ILD, but chest physical examination findings can be normal. Wheezing and fever are uncommon findings in pediatric ILD. Cyanosis accompanied by a prominent P2 heart sound is indicative of severe disease with the development of secondary pulmonary hypertension. Anemia or hemoptysis suggests a pulmonary vascular disease or pulmonary hemosiderosis. Rashes or joint complaints are consistent with an underlying connective tissue disease.

**DIAGNOSIS**

**Radiography**
Chest radiographic abnormalities can be classified as interstitial, reticular, nodular, reticulonodular, or honeycombed. The chest radiographic appearance may also be normal despite significant clinical impairment and may correlate poorly with the extent of disease. HRCT of the chest better defines the extent and distribution of disease and can provide specific information for selection of a biopsy site. Volume-controlled full-inspiratory and end-expiratory protocols used during HRCT can provide more information, possibly showing air trapping, ground-glass patterns, mosaic patterns of attenuation, hyperinflation, bronchiectasis, cysts, and/or nodular opacities. Serial HRCT scans have been beneficial in monitoring disease progression and severity.

**Pulmonary Function Tests**
Pulmonary function tests are important in defining the degree of pulmonary dysfunction and in following the response to treatment. In ILD, pulmonary function abnormalities demonstrate a restrictive ventilatory deficit with decreased lung volumes and reduced lung compliance. The functional residual capacity is often reduced but is usually less affected than vital capacity and total lung capacity. The residual volume is usually maintained; therefore, ratios of functional residual capacity: total lung capacity and residual volume: total lung capacity are increased. Diffusion capacity of the lung is often reduced. Exercise testing may detect pulmonary dysfunction, even in the early stage of ILD with a decline in oxygen saturation.

**Bronchoalveolar Lavage**
BAL may provide helpful information regarding secondary infection, bleeding, and aspiration and allows cytology and molecular analyses. Evaluation of cell counts, differential, and lymphocyte markers may be helpful in determining the presence of hypersensitivity pneumonitis or sarcoid. Although BAL does not usually determine the exact diagnosis, it can be diagnostic for disorders such as pulmonary alveolar proteinosis. Lung biopsy for histopathology by conventional thoracotomy or video-assisted thoracoscopy is usually the final step and is often necessary for a diagnosis. Biopsy may have a lower diagnostic yield in young children because of heterogeneous lung changes and often nonspecific histologic findings. Genetic testing for surfactant dysfunction mutational analysis is available. Evaluation for possible systemic disease may also be necessary.

**TREATMENT**
Supportive care of patients with ILD is essential and includes supplemental oxygen for hypoxia and adequate nutrition for growth failure. Antimicrobial treatment may be necessary for secondary infections. Some children may receive symptomatic relief from the use of bronchodilators. Antiinflammatory treatment with corticosteroids remains the initial treatment of choice. Controlled trials in children are lacking, however, and the clinical responses reported in case studies are variable. The usual dose of prednisone is 1-2 mg/kg/24 hr for 6-8 wks with tapering of dosage dictated by clinical response. Alternative, but not adequately evaluated, agents include hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, methotrexate, intravenous immunoglobulin, granulocyte-macrophage colony-stimulating factor, and pulsed high-dose steroids. Investigational approaches involve specific agents directed against the action of cytokines, growth factors, or oxidants. Lung transplantation for progressive or end-stage ILD is successful in some infants and children. Appropriate treatment for underlying systemic disease is indicated. Preventive measures include avoidance of all inhalation irritants, such as tobacco smoke and, when appropriate, molds and bird antigens. Supervised pulmonary rehabilitation programs may be helpful.

**Genetic Counseling**
A high incidence of ILD in some families suggests a genetic predisposition to either development of the disease or severity of the disorder. Genetic counseling may be beneficial if a positive familial history is obtained.

**PROGNOSIS**
The overall mortality of ILD is very variable and depends on specific diagnosis. Some children recover spontaneously without treatment, but other children steadily progress to death. Pulmonary hypertension, failure to thrive, and severe fibrosis are considered poor prognostic indicators.

**GOODPASTURE DISEASE**
Goodpasture disease is the prototypical immunologic mediated interstitial lung disease (see Chapter 517). Because of the concurrent presentation of renal and pulmonary disease, the differential diagnosis focuses on distinguishing Goodpasture disease from GPA, microscopic polyangiitis, Henoch-Schönlein purpura, and idiopathic pulmonary hemorrhage syndromes.

**Pathophysiology**

**Immunology Factors**
The development of anti–glomerular basement membrane (anti-GBM) antibodies directly correlates with the development of pulmonary and renal disease. Removal of such antibodies by plasmapheresis results in improvement of the disease process in some patients but not in all. The anti-GBM antibodies are IgG1 and IgG4 complement-bind ing subclasses of IgG which activate complement. Complement fragments signal the recruitment of neutrophils and macrophage in both the lung and kidney basement membranes resulting in damage and capillaritis.

**Genetic Factors**
Genetics appears to contribute strongly to the development of this disease with the presence of major histocompatibility complex class II alleles DR15, DR4, DRB1*1501, DRB1*04, and DRB1*03 predisposing to disease.
Environmental Factors
Exposure to smoke appears to be a strong factor in the development of Goodpasture disease. Whether smoking alters the ultrastructure of the basement membrane or exogenous particles or noxious substances in smoke alter the type IV collagen is unknown. Smokers are more likely to develop pulmonary hemorrhage than non-smokers who have Goodpasture disease. Other injuries to the alveoli from infection, hydrocarbon inhalation, or cocaine inhalation have been reported as associated events prior to development of Goodpasture disease.

Clinical Manifestations
The majority of patients present with many days or weeks of cough, dyspnea, fatigue, and sometimes hemoptysis. Young children tend to swallow small amounts of blood from hemoptysis and may present with vomiting blood. Occasionally, the hemoptysis is large and resultant anemia is a consequence of large quantities of blood loss. Renal compromise is found with abnormal renal function tests. Younger patients tend to present with both the pulmonary and renal syndrome concurrently. Adults are less likely to develop pulmonary disease.

Laboratory
Serologic detection of anti-GBM antibodies are positive in more than 90% of patients with Goodpasture disease. A complete blood count will show anemia that is normocytic and normochromic as seen in chronic inflammatory disease. Urinalysis may reveal hematuria and proteinuria and blood tests demonstrate renal compromise with elevated blood urea nitrogen and creatinine.

Studies for pANCA (antimyeloperoxidase ANCA) should also be performed and are positive in approximately 25-30% of patients concurrently with anti-GBM antibodies. Clinical disease may be more difficult to treat and the presence of these antibodies may herald a more severe form of disease.

Chest Radiography
Chest radiography in Goodpasture disease will often show widely scattered patches of pulmonary infiltrates. If these infiltrates are in the periphery of the lung, they may be difficult to distinguish from the eosinophilic lung diseases. Interstitial patterns of thickening may be found as well. HRCT is usually not performed in this disease as the constellation of pulmonary hemorrhage, renal compromise, and positive serologic tests with anti-GBM antibodies detected often preclude the need for this test.

Pulmonary Function Testing
Pulmonary spirometry often reveals a restrictive defect with reduction in forced vital capacity and forced expiratory volume at 1-second. DLCO is a valuable test when pulmonary hemorrhage is a strong consideration. The intent of this test is to measure the ability of the lung to transfer inhaled gas to the red blood cell in the pulmonary capillary bed. This takes advantage of the hemoglobin’s high affinity to bind carbon monoxide. It was once thought that reduction of DLCO was a measure of reduced surface area of the alveoli. Current data suggests that it directly correlates with the volume of blood in the pulmonary capillary bed. In pulmonary hemorrhage syndromes, blood in the alveoli plus the blood in the capillary bed increase the DLCO significantly and should alert the clinician to the possibility of pulmonary hemorrhage.

Bronchoscopy and Bronchoalveolar Lavage
Pulmonary abnormalities can often be best assessed by a bronchoscopy with BAL. The visual presence of blood on inspection as well as BAL will be obvious. Infections must be ruled out in many cases, and this technique adds significant value. BAL cell count will show hemosiderin-laden macrophage that have engulfed and broken down the red blood cells, leaving iron in these cells.

Lung Biopsy
Lung biopsy in patients with active disease reveals capillaritis from neutrophils, hemosiderin-laden macrophages, type II pneumocyte hyperplasia, and interstitial thickening at the level of the alveolus. Staining for IgG and complement is found by immunofluorescence in along the basement membrane in a linear pattern. This antibody deposition pattern led to the investigation of endogenous antigens in the basement membrane.

Treatment
More than half of patients with Goodpasture disease who forego treatment die within 2 yr from either respiratory failure, renal failure, or both. After a diagnosis is made, therapy with corticosteroids (e.g., prednisone, 1 mg/kg/day) coupled with oral cyclophosphamide (2.5 mg/kg/day) is begun. The addition of daily plasmapheresis for 2 wks may accelerate improvement. Cyclophosphamide may be discontinued after 2-3 mo. Steroids are often weaned over a 6-9 mo period. Survival is affected by the need for ongoing dialysis. Patients who do not require persistent dialysis have a survival rate at 1 yr of 80% or more.

Bibliography is available at Expert Consult.
Bibliography


Chapter 400
Community-Acquired Pneumonia
Matthew S. Kelly and Thomas J. Sandora

EPIDEMIOLOGY
Pneumonia, defined as inflammation of the lung parenchyma, is the leading cause of death globally among children younger than age 5 yr, accounting for an estimated 1.2 million (18% total) deaths annually (Fig. 400-1). The incidence of pneumonia is more than 10-fold higher (0.29 episodes vs 0.03 episodes), and the number of childhood-related deaths from pneumonia ≈2,000 fold higher, in developing than in developed countries (Table 400-1). Fifteen countries account for more than three-fourths of all pediatric deaths from pneumonia.

In the United States from 1939-1996, pneumonia mortality in children declined by 97%; in 1970, pneumonia accounted for 9% of all deaths of children younger than age 5 yr compared to 2% in 2007. It is probable that this decline results from the introduction of antibiotics, vaccines, and the expansion of medical insurance coverage for children. Haemophilus influenzae type b (see Chapter 194) was an important cause of bacterial pneumonia in young children but became uncommon with the routine use of effective vaccines, while measles vaccine greatly reduced the incidence of measles-related pneumonia deaths in developing countries. Improved access to healthcare in rural areas of developing countries and the introduction of pneumococcal conjugate vaccines (see Chapter 182) were also important contributors to the further reductions in pneumonia-related deaths achieved over the past decade.

ETIOLOGY
Although most cases of pneumonia are caused by microorganisms, noninfectious causes include aspiration (of food or gastric acid, foreign bodies, hydrocarbons, and lipid substances), hypersensitivity reactions, and drug- or radiation-induced pneumonitis. The cause of pneumonia in an individual patient is often difficult to determine because direct culture of lung tissue is invasive and rarely performed. Cultures performed on specimens in children obtained from the upper respiratory tract or sputum typically do not accurately reflect the cause of lower respiratory tract infection. With the use of molecular diagnostic testing, a bacterial or viral cause of pneumonia can be identified in
40-80% of children with community-acquired pneumonia. Streptococcus pneumoniae (pneumococcus) is the most common bacterial pathogen in children 3 wk to 4 yr of age, whereas Mycoplasma pneumoniae and Chlamydia pneumoniae are the most frequent bacterial pathogens in children age 5 yr and older. In addition to pneumococcus, other bacterial causes of pneumonia in previously healthy children in the United States include group A streptococcus (Streptococcus pyogenes) and Staphylococcus aureus (see Chapter 181.1 and Table 400-2). S. aureus pneumonia often complicates an illness caused by influenza viruses. S. pneumoniae, H. influenzae, and S. aureus are the major causes of hospitalization and death from bacterial pneumonia among children in developing countries, although in children with HIV infection, Mycobacterium tuberculosis (see Chapter 215), atypical mycobacteria, Salmonella (see Chapter 198), Escherichia coli (see Chapter 200), and Pneumocystis jiroveci (see Chapter 244) must be considered. The incidence of pneumonia caused by H. influenzae or S. pneumoniae has been significantly reduced in areas where routine immunization has been implemented.

Viral pathogens are a prominent cause of lower respiratory tract infections in infants and children older than 1 mo but younger than 5 yr of age. Viruses can be detected in 40-80% of children with pneumonia using molecular diagnostic methods. Of the respiratory viruses, respiratory syncytial virus (RSV) (see Chapter 260) and rhinoviruses are the most commonly identified pathogens, especially in children younger than 2 yr of age. However, the role of rhinoviruses in severe lower respiratory tract infection remains poorly defined as these viruses are frequently detected in infections with 2 or more pathogens and among asymptomatic children. Other common viruses causing pneumonia include influenza virus (see Chapter 258), parainfluenza viruses, adenoviruses, enteroviruses, and human metapneumovirus. Infection with more than 1 respiratory virus occurs in up to 20% of cases. The age of the patient may help identify possible pathogens (Table 400-3).

Lower respiratory tract viral infections are much more common in the fall and winter in both the northern and southern hemispheres in relation to the seasonal epidemics of respiratory viral infection that occur each year. The typical pattern of these epidemics usually begins in the fall, when parainfluenza infections appear and most often manifest as croup. Later in winter, RSV, human metapneumovirus, and influenza viruses cause widespread infection, including upper respiratory tract infections, bronchiolitis, and pneumonia. RSV is particularly severe among infants and young children, whereas influenza virus causes disease and excess hospitalization for acute respiratory illness in all age groups. Knowledge of the prevailing viral epidemic may lead to a presumptive initial diagnosis.

Immunization status is relevant because children fully immunized against H. influenzae type b and S. pneumoniae are less likely to be infected with these pathogens. Children who are immunosuppressed or who have an underlying illness may be at risk for specific pathogens, such as Pseudomonas spp. in patients with cystic fibrosis (see Chapter 403).

**PATHOGENESIS**

The lower respiratory tract is normally kept sterile by physiologic defense mechanisms, including mucociliary clearance, the properties of normal secretions such as secretory immunoglobulin (Ig) A, and

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**Table 400-1** Incidence of Pneumonia Cases and Pneumonia Deaths Among Children Younger Than Age 5 Yr, by UNICEF Region, 2004*

<table>
<thead>
<tr>
<th>UNICEF REGIONS</th>
<th>NUMBER OF CHILDREN YOUNGER THAN 5 YR OF AGE (IN THOUSANDS)</th>
<th>NUMBER OF CHILDHOOD PNEUMONIA DEATHS (IN THOUSANDS)</th>
<th>INCIDENCE OF PNEUMONIA CASES (EPISODES PER CHILD PER YEAR)</th>
<th>TOTAL NUMBER OF PNEUMONIA EPISODES (IN THOUSANDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asia</td>
<td>169,300</td>
<td>702</td>
<td>0.36</td>
<td>61,300</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>117,300</td>
<td>1,022</td>
<td>0.30</td>
<td>35,200</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>43,400</td>
<td>82</td>
<td>0.26</td>
<td>11,300</td>
</tr>
<tr>
<td>East Asia and Pacific</td>
<td>146,400</td>
<td>158</td>
<td>0.24</td>
<td>34,500</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>56,500</td>
<td>50</td>
<td>0.22</td>
<td>12,200</td>
</tr>
<tr>
<td>Central and Eastern Europe and the Commonwealth of Independent States</td>
<td>26,400</td>
<td>29</td>
<td>0.09</td>
<td>2,400</td>
</tr>
<tr>
<td>Developing countries</td>
<td>533,000</td>
<td>2,039</td>
<td>0.29</td>
<td>154,500</td>
</tr>
<tr>
<td>Industrialized countries</td>
<td>54,200</td>
<td>1</td>
<td>0.03</td>
<td>1,600</td>
</tr>
<tr>
<td>World</td>
<td>613,600</td>
<td>2,044</td>
<td>0.26</td>
<td>158,500</td>
</tr>
</tbody>
</table>

*Regional estimates in Columns 2, 3, and 5 do not add up to the world total because of rounding.

Table 400-2 | Causes of Infectious Pneumonia

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>Group B streptococcus, Escherichia coli, other Gram-negative bacilli, Streptococcus pneumoniae, Haemophilus influenzae (type b,* nontypeable)</td>
</tr>
<tr>
<td>3 wk-3 mo</td>
<td>Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), S. pneumoniae, H. influenzae (type b,* nontypeable); if patient is afebrile, consider Chlamydia trachomatis</td>
</tr>
<tr>
<td>≥5 yr</td>
<td>M. pneumoniae, S. pneumoniae, Chlamyphila pneumoniae, H. influenzae (type b,* nontypeable), Mycoplasma pneumoniae, group A streptococcus</td>
</tr>
</tbody>
</table>

*R. pneumoniae type b is uncommon with routine H. influenzae type b immunization.


clearing of the airway by coughing. Immunologic defense mechanisms of the lung that limit invasion by pathogenic organisms include macrophages that are present in alveoli and bronchioles, secretary IgA, and other immunoglobulins. Trauma, anesthesia, and aspiration increase the risk of pulmonary infection.

Viral pneumonia usually results from spread of infection along the airways, accompanied by direct injury of the respiratory epithelium, which results in airway obstruction from swelling, abnormal secretions, and cellular debris. The small caliber of airways in young infants makes such patients particularly susceptible to severe infection. Atelectasis, interstitial edema, and ventilation–perfusion mismatch causing significant hypoxemia often accompany airway obstruction. Viral infection of the respiratory tract can also predispose to secondary bacterial infection by disturbing normal host defense mechanisms, altering secretions, and modifying the bacterial flora.

Bacterial pneumonia most often occurs when respiratory tract organisms colonize the trachea and subsequently gain access to the lungs, but pneumonia may also result from direct seeding of lung tissue after bacteraemia. When bacterial infection is established in the lung parenchyma, the pathologic process varies according to the invading organism. *M. pneumoniae* (see Chapter 223) attaches to the respiratory epithelium, inhibits ciliary action, and leads to cellular destruction and an inflammatory response in the submucosa. As the infection progresses, sloughed cellular debris, inflammatory cells, and mucus cause airway obstruction, with spread of infection occurring along the bronchial tree, as it does in viral pneumonia.

*S. pneumoniae* produces local edema that aids in the proliferation of organisms and their spread into adjacent portions of lung, often resulting in the characteristic focal lobar involvement.

Group A streptococcal infection of the lower respiratory tract results in more diffuse infection with interstitial pneumonia. The pathology includes necrosis of tracheobronchial mucosa; formation of large amounts of exudate, edema, and local hemorrhage, with extension into the interalveolar septa; and involvement of lymphatic vessels and the increased likelihood of pleural involvement.

*S. aureus* pneumonia manifests in confluent bronchopneumonia, which is often unilateral and characterized by the presence of extensive areas of hemorrhagic necrosis and irregular areas of cavitation of the lung parenchyma, resulting in pneumatoceles, empyema, or, at times, bronchopulmonary fistulas.
Recurrent pneumonia is defined as 2 or more episodes in a single year or 3 or more episodes ever, with radiographic clearing between occurrences. An underlying disorder should be considered if a child experiences recurrent pneumonia (Table 400-4).

CLINICAL MANIFESTATIONS

Pneumonia is frequently preceded by several days of symptoms of an upper respiratory tract infection, typically rhinitis and cough. In viral pneumonia, fever is usually present but temperatures are generally lower than in bacterial pneumonia. Tachypnea is the most consistent clinical manifestation of pneumonia. Increased work of breathing accompanied by intercostal, subcostal, and suprasternal retractions, nasal flaring, and use of accessory muscles is common. Severe infection may be accompanied by cyanosis and lethargy, especially in infants. Auscultation of the chest may reveal crackles and wheezing, but it is often difficult to localize the source of these adventitious sounds in young very young children with hyperresonant chests. It is often not possible to distinguish viral pneumonia clinically from disease caused by Mycoplasma and other bacterial pathogens.

Bacterial pneumonia in adults and older children typically begins suddenly with high fever, cough, and chest pain. Other symptoms that may be seen include drowsiness with intermittent periods of restlessness; rapid respirations; anxiety; and, occasionally, delirium. In many children, splinting on the affected side to minimize pleuritic pain and improve ventilation is noted; such children may lie on one side with the knees drawn up to the chest.

Physical findings depend on the stage of pneumonia. Early in the course of illness, diminished breath sounds, scattered crackles, and rhonchi are commonly heard over the affected lung field. With the development of increasing consolidation or complications of pneumonia such as pleural effusion or empyema, dullness on percussion is noted and breath sounds may be diminished. A lag in respiratory excursion often occurs on the affected side. Abdominal distention may be prominent because of gastric dilation from swallowed air or ileus. Abdominal pain is common in lower-lobe pneumonia. The liver may seem enlarged because of downward displacement of the diaphragm secondary to hyperinflation of the lungs or superimposed congestive heart failure.


diagnosis

S summoning symptoms described in adults with pneumococcal pneumonia may be noted in older children but are rarely observed in infants and young children, in whom the clinical pattern is considerably more variable. In infants, there may be a prodrome of upper respiratory tract infection and diminished appetite, leading to the abrupt onset of fever, restlessness, apprehension, and respiratory distress. These infants appear ill, with respiratory distress manifested as grunting; nasal flaring; retractions of the supraclavicular, intercostal, and subcostal areas; tachypnea; tachycardia; air hunger; and often cyanosis. Results of physical examination may be misleading, particularly in young infants, with meager findings disproportionate to the degree of tachypnea. Some infants with bacterial pneumonia may have associated gastrointestinal disturbances characterized by vomiting, anorexia, diarrhea, and abdominal distention secondary to a paralytic ileus. Rapid progression of symptoms is characteristic in the most severe cases of bacterial pneumonia.

Diagnosis

An infiltrate on chest radiograph (posteroanterior and lateral views) supports the diagnosis of pneumonia; the film may also indicate a complication such as a pleural effusion or empyema. Viral pneumonia is usually characterized by hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing (Fig. 400-2). Confluent lobar consolidation is typically seen with pneumococcal pneumonia (Fig. 400-3). The radiographic appearance alone is not diagnostic, and other clinical features must be considered. Repeat chest radiographs are not required for proof of cure for patients with uncomplicated pneumonia. Some
Part in fever. old pneumococcal findings Factors Suggesting Need for pneumonia characteristic Respiratory cough and a 14 boy of 400-3 are also suggestive of a bacterial etiology. effusion, lobar consolidation, and a high fever at the onset of the illness 40,000/mm3, and a predominance of granulocytes. A large pleural effusion, lobar consolidation, and a high fever at the onset of the illness are also suggestive of a bacterial etiology. Atypical pneumonia caused by C. pneumoniae or M. pneumoniae is difficult to distinguish from pneumococcal pneumonia on the basis of radiographic and laboratory findings, and although pneumococcal pneumonia is associated with a higher WBC count, erythrocyte sedimentation rate, procalcitonin, and C-reactive protein level, there is considerable overlap, particularly with adenoviruses and enteroviruses.

The definitive diagnosis of a viral infection rests on the isolation of a virus or detection of the viral genome or antigen in respiratory tract secretions. Reliable DNA or RNA tests for the rapid detection of many respiratory pathogens, such as mycoplasma, pertussis, and viruses, including RSV, parainfluenza, influenza, and adenoviruses, are available and accurate. Serologic techniques can also be used to diagnose a recent respiratory viral infection but generally require testing of acute and convalescent serum samples for a rise in antibodies to a specific viral agent. This diagnostic technique is laborious, slow, and not generally clinically useful because the infection usually resolves by the time it is confirmed serologically. Serologic testing may be valuable as an epidemiologic tool to define the incidence and prevalence of the various respiratory viral pathogens. Patient peripheral cell gene expression patterns determined by microarray reverse transcription polymerase chain reaction is an emerging technology that may help differentiate viral from bacterial causes of pneumonia.

The definitive diagnosis of a bacterial infection requires isolation of an organism from the blood, pleural fluid, or lung. Culture of sputum is of little value in the diagnosis of pneumonia in young children, while percutaneous lung aspiration is invasive and not routinely performed. Blood culture results are positive in only 10% of children with pneumococcal pneumonia and are not recommended for nontoxic appearing children treated as an outpatient. Blood cultures are recommended for those who fail to improve or have clinical deterioration, in those with complicated pneumonia (Table 400-5) and those requiring hospitalization. Cold agglutinins at titer >1:64 are found in the blood in ≈50% of patients with M. pneumoniae infections. Cold agglutinin findings are nonspecific because other pathogens such as influenza viruses may also cause increases. Acute infection caused by M. pneumoniae can be diagnosed on the basis of a positive polymerase chain reaction test result or seroconversion in an IgG assay. Serologic evidence, such as the antistreptolysin O titer, may be useful in the diagnosis of group A streptococcal pneumonia.

**TREATMENT**

Treatment of suspected bacterial pneumonia is based on the presumptive cause and the age and clinical appearance of the child. For mildly ill children who do not require hospitalization, amoxicillin is recommended. With the emergence of penicillin-resistant pneumococci, high doses of amoxicillin (80-90 mg/kg/24 hr) should be prescribed unless local data indicate a low prevalence of resistance. Therapeutic alternatives include cefuroxime axetil and amoxicillin/clavulanate. For school-age children and in children in whom infection with M. pneumoniae or C. pneumoniae is suggested, a macrolide antibiotic such as

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**Table 400-5** Factors Suggesting Need for Hospitalization of Children with Pneumonia

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;6 mo</td>
</tr>
<tr>
<td>Sickle cell anemia with acute chest syndrome</td>
</tr>
<tr>
<td>Multiple lobe involvement</td>
</tr>
<tr>
<td>Immuno compromised state</td>
</tr>
<tr>
<td>Toxic appearance</td>
</tr>
<tr>
<td>Moderate to severe respiratory distress</td>
</tr>
<tr>
<td>Requirement for supplemental oxygen</td>
</tr>
<tr>
<td>Complicated pneumonia*</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Vomiting or inability to tolerate oral fluids or medications</td>
</tr>
<tr>
<td>No response to appropriate oral antibiotic therapy</td>
</tr>
<tr>
<td>Social factors (e.g., inability of caregivers to administer medications at home or follow-up appropriately)</td>
</tr>
</tbody>
</table>

*Pleural effusion, empyema, abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory distress syndrome, extrapulmonary infection (meningitis, arthritis, pericarditis, osteomyelitis, endocarditis), hemolytic uremic syndrome, sepsis.


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**Figure 400-3** Radiographic findings characteristic of pneumococcal pneumonia in a 14 yr old boy with cough and fever. Posteroanterior (A) and lateral (B) chest radiographs reveal consolidation in the right lower lobe, strongly suggesting bacterial pneumonia.
azithromycin is an appropriate choice. In adolescents, a respiratory fluoroquinolone (levofloxacin, moxifloxacin) may be considered as an alternative. Despite substantial gains over the past decade, in developing countries only ≈60% of children with symptoms of pneumonia (≈50% in sub-Saharan Africa) are taken to an appropriate caregiver, and less than one-third receive antibiotics. The World Health Organization and other international groups have developed systems to train mothers and local healthcare providers in the recognition and treatment of pneumonia.

The empiric treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on the clinical manifestations at the time of presentation. In areas without substantial high-level penicillin resistance among *S. pneumoniae*, children who are fully immunized against *H. influenzae* type b and *S. pneumoniae* and are not severely ill should receive amoxicillin or penicillin G. For children who do not meet these criteria, ceftriaxone or cefotaxime should be used. If clinical features suggest staphylococcal pneumonia (pneumatoceles, empyema), initial antimicrobial therapy should also include vancomycin or clindamycin.

If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for those patients who are mildly ill, have clinical evidence suggesting viral infection, and are in no respiratory distress. However, up to 30% of patients with known viral infection, particularly influenza viruses, may have coexisting bacterial pathogens. Therefore, if the decision is made to withhold antibiotic therapy on the basis of presumptive diagnosis of a viral infection, deterioration in clinical status should signal the possibility of superimposed bacterial infection, and antibiotic therapy should be initiated.

Table 400-5 notes the indications for admission to a hospital. The optimal duration of antibiotic treatment for pneumonia has not been well-established in controlled studies. However, antibiotics should generally be continued until the patient has been afebrile for 72 hr, and the total duration should not be less than 10 days (or 5 days if azithromycin is used). Shorter courses (5-7 days) may also be effective, particularly for children managed on an outpatient basis, but further study is needed. Available data do not support prolonged courses of treatment for uncomplicated pneumonia. In developing countries, oral zinc (10 mg/day for <12 mo, 20 mg/day for ≥12 mo) reduces mortality among children with clinically defined severe pneumonia.

**PROGNOSIS**

Typically, patients with uncomplicated community-acquired bacterial pneumonia show response to therapy, with improvement in clinical symptoms (fever, cough, tachypnea, chest pain), within 48-96 hr of initiation of antibiotics. Radiographic evidence of improvement lags substantially behind clinical improvement. A number of possibilities must be considered when a patient does not improve with appropriate antibiotic therapy: (1) complications, such as empyema (see Table 400-5); (2) bacterial resistance; (3) nonbacterial etiologies such as viruses or fungi and aspiration of foreign bodies or food; (4) bronchial obstruction from endobronchial lesions, foreign body, or mucous plugs; (5) preexisting diseases such as immunodeficiencies, ciliary dyskinesia, cystic fibrosis, pulmonary sequestration, or congenital pulmonary airway malformation, formerly called cystic adenomatoid malformation; and (6) other noninfectious causes (including bronchiolitis obliterans, hypersensitivity pneumonitis, eosinophilic pneumonia, aspiration, and granulomatosis with polyangiitis, formerly called Wegener granulomatosis). A repeat chest radiograph is the first step in determining the reason for delay in response to treatment. Bronchoalveolar lavage may be indicated in children with respiratory failure; high-resolution CT scans may better identify complications or an anatomic reason for a poor response to therapy.

Mortality from community-acquired pneumonia in developed nations is rare, and most children with pneumonia do not experience long-term pulmonary sequelae. Some data suggest that up to 45% of children have symptoms of asthma 5 yr after hospitalization for pneumonia; this finding may reflect either undiagnosed asthma at the time of presentation or a propensity for development of asthma after pneumonia.

**COMPLICATIONS**

Complications of pneumonia (see Table 400-5) are usually the result of direct spread of bacterial infection within the thoracic cavity (pleural effusion, empyema, and pericarditis) or bacteremia and hematologic spread (Fig. 400-4). Meningitis, supplicative arthritis, and osteomyelitis are rare complications of hematologic spread of pneumococcal or *H. influenzae* type b infection.

*S. aureus*, *S. pneumoniae*, and *S. pyogenes* are the most common causes of parapneumonic effusions and empyema (Table 400-6). Nonetheless many effusions that complicate bacterial pneumonia are sterile. Universal 16S ribosomal RNA gene polymerase chain reaction identifies the bacterial genome and can determine the bacterial etiology of the effusion if the culture is negative. The treatment of empyema is based on the stage (exudative, fibrinopurulent, organizing). Imaging studies including ultrasonography and CT are helpful in determining the stage of empyema. The mainstays of therapy include antibiotic therapy and drainage with tube thoracostomy. Additional effective approaches include the use of intrapleural fibrinolytic therapy (urokinase, streptokinase, tissue plasminogen activator) and selected video-assisted thoracoscopic surgery to debride or lyse adhesions and drain loculated areas of pus. Early diagnosis and intervention, particularly with fibrinolysis or less often video-assisted thoracoscopy, may obviate the need for thoracotomy and open debridement. Fibrinolysis is more cost-effective than video-assisted thoracoscopy.

**PREVENTION**

Some evidence exists to suggest that vaccination has reduced the incidence of pneumonia hospitalizations. The annual rate of all-cause pneumonia hospitalization among children younger than 2 yr of age in the United States during the period 1997-1999 was 12.5 per 1,000 children. In February 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was licensed and recommended. In 2006, the pneumonia hospitalization rate in this age group was 8.1 per 1,000 children, a 35% decrease from the prevaccine rate. Although these data do not establish that PCV7 directly reduced pneumonia hospitalization rates,
Table 400-6  Differentiation of Pleural Fluid

<table>
<thead>
<tr>
<th></th>
<th>TRANSUDATE</th>
<th>EMPYEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Clear</td>
<td>Cloudy or purulent</td>
</tr>
<tr>
<td>Cell count (per mm³)</td>
<td>&lt;1,000</td>
<td>Often &gt;50,000 (cell count has limited predictive value)</td>
</tr>
<tr>
<td>Cell type</td>
<td>Lymphocytes, monocytes</td>
<td>Polymorphonuclear leukocytes (neutrophils)</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>&lt;200 U/L</td>
<td>More than two-thirds upper limit of normal for serum lactate dehydrogenase (LDH)</td>
</tr>
<tr>
<td>Pleural fluid: serum LDH ratio</td>
<td>&lt;0.6</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>Protein &gt;3 g</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Pleural fluid: serum protein ratio</td>
<td>&lt;0.5</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Glucose*</td>
<td>Normal</td>
<td>Low (&lt;40 mg/dL)</td>
</tr>
<tr>
<td>pH*</td>
<td>Normal (7.40-7.60)</td>
<td>&lt;7.10</td>
</tr>
<tr>
<td>Gram stain</td>
<td>Negative</td>
<td>Occasionally positive (less than one-third of cases)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&gt;55 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Pleural cholesterol: serum cholesterol ratio</td>
<td>&lt;0.3</td>
<td>&gt;0.3</td>
</tr>
</tbody>
</table>

*Low glucose or pH may be seen in malignant effusion, tuberculosis, esophageal rupture, pancreatitis (positive pleural amylase), and rheumatologic diseases (e.g., systemic lupus erythematosus).


they do suggest that vaccination has resulted in a sustained benefit in preventing hospitalization for young children with pneumonia.

In 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States; it may prevent even more cases of pneumococcal disease not covered by the PCV7 vaccine.

The expansion of influenza vaccine recommendations to include all children >6 mo of age in 2010 might be expected to affect pneumonia hospitalization rates in a similar fashion, and ongoing surveillance is warranted.

Bibliography is available at Expert Consult.
Chapter 400  Community-Acquired Pneumonia 2094.e1

Bibliography


Bronchiectasis is characterized by irreversible abnormal dilation and anatomic distortion of the bronchial tree and represents a common end stage of a many nonspecific and unrelated antecedent events. Its incidence has been decreasing overall in industrialized countries, but it persists as a problem in lower and middle income countries and among some ethnic groups in industrialized nations. Females are afflicted more frequently than males.

**PATHOPHYSIOLOGY AND PATHOGENESIS**

In industrialized nations, cystic fibrosis (see Chapter 403) is the most common cause of clinically significant bronchiectasis. Other conditions associated with bronchiectasis include primary ciliary dyskinesia (see Chapter 404), foreign-body aspiration (see Chapter 387), aspiration of gastric contents, immune deficiency syndromes (especially humoral immunity), and infection, especially pertussis, measles, and tuberculosis (Table 401-1). Bronchiectasis can also be congenital, as in

<table>
<thead>
<tr>
<th>Table 401-1</th>
<th>Conditions That Predispose to Bronchiectasis in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROXIMAL AIRWAY NARROWING</strong></td>
<td></td>
</tr>
<tr>
<td>Airway wall compression (i.e., vascular ring, adenopathy impinging on airways)</td>
<td></td>
</tr>
<tr>
<td>Airway intraluminal obstruction (e.g., inhaled foreign body, granulation tissue)</td>
<td></td>
</tr>
<tr>
<td>Airway stenosis and malacia</td>
<td></td>
</tr>
<tr>
<td><strong>AIRWAY INJURY</strong></td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis obliterans (e.g., postviral, after lung transplantation)</td>
<td></td>
</tr>
<tr>
<td>Recurrent pneumonitis or pneumonia (e.g., pneumococcal pneumonia, aspiration pneumonia)</td>
<td></td>
</tr>
<tr>
<td><strong>ALTERED PULMONARY HOST DEFENSES</strong></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>Ciliary dyskinesia</td>
<td></td>
</tr>
<tr>
<td>Impaired cough (e.g., neuromuscular weakness conditions)</td>
<td></td>
</tr>
<tr>
<td><strong>ALTERED IMMUNE STATES</strong></td>
<td></td>
</tr>
<tr>
<td>Primary abnormalities (e.g., hypogammaglobulinemia)</td>
<td></td>
</tr>
<tr>
<td>Secondary abnormalities (e.g., HIV infection, immunosuppressive agents)</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td></td>
</tr>
<tr>
<td>Plastic bronchitis</td>
<td></td>
</tr>
</tbody>
</table>


**Williams-Campbell syndrome**, in which there is an absence of annular bronchial cartilage, and **Marnier-Kuhn syndrome** (congenital tracheobronchomegaly), in which there is a connective tissue disorder. Other disease entities associated with bronchiectasis are **right middle lobe syndrome** (chronic extrinsic compression of right middle lobe bronchus by hilar lymph nodes) and **yellow nail syndrome** (pleural effusion, lymphedema, discolored nails).

Three basic mechanisms are involved in the pathogenesis of bronchiectasis. Obstruction can occur because of tumor, foreign body, impacted mucus because of poor mucociliary clearance, external
compression, bronchial webs, and atresia. Infections caused by *Bordetella pertussis*, measles, rubella, togavirus, respiratory syncytial virus, adenovirus, and *Mycobacterium tuberculosis* induce chronic inflammation, progressive bronchial wall damage, and dilation. Chronic inflammation similarly contributes to the mechanism by which obstruction leads to bronchiectasis. Activation of toll-like receptors results in the activation of nuclear factor κB and the release of proinflammatory cytokines interleukin (IL)-1β, IL-8, and tumor necrosis factor-α. IL-8 is a chemoattractant for neutrophils, which are the main inflammatory cell involved in the pathogenesis of bronchiectasis. Once activated, neutrophils produce neutrophil elastase and matrix metalloproteinases, MMP-8 and MMP-9. IL-6, IL-8, and tumor necrosis factor-α are elevated in the airways of patients with bronchiectasis. The mechanism by which bronchiectasis occurs in congenital forms is likely related to abnormal cartilage formation. The common thread in the pathogenesis of bronchiectasis consists of difficulty clearing secretions and recurrent infections with a “vicious cycle” of infection and inflammation resulting in airway injury and remodeling.

Bronchiectasis can manifest in any combination of three pathologic forms, best defined by high-resolution CT (HRCT) scan. In cylindrical bronchiectasis, the bronchial outlines are regular, but there is diffuse dilation of the bronchial unit. The bronchial lumen ends abruptly because of mucous plugging. In varicose bronchiectasis, the degree of dilation is greater, and local constrictions cause an irregularity of outline resembling that of varicose veins. There may also be small sacculations. In sacculary (cystic) bronchiectasis, bronchial dilation progresses and results in ballooning of bronchi that end in fluid- or mucus-filled sacs. This is the most severe form of bronchiectasis. Bronchiectasis lies within a disease spectrum of chronic pediatric suppurative lung disease. The following definitions have been proposed: prebronchiectasis (chronic or recurrent endobronchial infection with nonspecific HRCT changes; may be reversible); HRCT bronchiectasis (clinical symptoms with HRCT evidence of bronchial dilation; may persist, progress, or improve and resolve); established bronchiectasis (like the previous but with no resolution within 2 yr). Early diagnosis and aggressive therapy are important to prevent the development of established bronchiectasis.

**CLINICAL MANIFESTATIONS**

The most common complaints in patients with bronchiectasis are cough and production of copious purulent sputum. Younger children may swallow the sputum. Hemoptysis is seen with some frequency. Fever can occur with infectious exacerbations. Anorexia and poor weight gain may occur as time passes. Physical examination typically reveals crackles localized to the affected area, but wheezing as well as digital clubbing may also occur. In severe cases, dyspnea and hypoxemia can occur. Pulmonary function studies may demonstrate an obstructive, restrictive, or mixed pattern. Typically, impaired diffusion capacity is a late finding.

**DIAGNOSIS**

Conditions that can be associated with bronchiectasis should be ruled out by appropriate investigations (e.g., sweat test, immunologic workup). Chest radiographs of patients with bronchiectasis tend to be nonspecific. Typical findings can include increase in size and loss of definition of bronchovascular markings, crowding of bronchi, and loss of lung volume. In more severe forms, cystic spaces, occasionally with air–fluid levels and honeycombing, may occur. Compensatory overinflation of unaffected lung may be seen. Thin-section HRCT scanning is the gold standard, because it has excellent sensitivity and specificity. CT provides further information on disease location, presence of mediastinal lesions, and the extent of segmental involvement. The addition of radiolabeled aerosol inhalation to CT scanning can provide even more information. The CT findings in patients with bronchiectasis typically include cylindrical (“tram lines,” “signet ring appearance”), varicose (bronchi with “beaded contour”), cystic (cysts in “strings and clusters”), or mixed forms (Fig. 401-1). The lower lobes are most commonly affected.
TREATMENT
The initial therapy for patients with bronchiectasis is medical and aims at decreasing airway obstruction and controlling infection. Chest physiotherapy (postural drainage), antibiotics, and bronchodilators are essential. Two to 4 wk of parenteral antibiotics is often necessary to manage acute exacerbations adequately. Exacerbations can be defined as the presence of 1 major criteria (wet cough enduring longer than 72 hr, increased cough frequency over 72 hr) plus 1 laboratory criteria (C-reactive protein >3 mg/L, serum IL-6 >2 ng/L, serum amyloid A >5 mg/L, elevated neutrophil percentage), 2 major criteria, or 1 major criteria plus 2 minor criteria (change in sputum color, breathlessness, chest pain, crackles/crepitations, wheeze). Antibiotic choice is dictated by the identification and sensitivity of organisms found on deep throat, sputum (induced or spontaneous), or bronchoalveolar lavage fluid cultures. The most common organisms found in children with bronchiectasis include *Streptococcus pneumoniae*, *Haemophilus influenzae* non-type b, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae*. Amoxicillin/clavulanic acid (22.5 mg/kg/dose twice daily) has been particularly successful at treating most pulmonary exacerbations. Long-term prophylactic oral (macrolide) or nebulized antibiotics (e.g., tobramycin, colistin, aztreonam) may be beneficial. Airway hydration (inhaled hypertonic saline or mannitol) also improves quality of life in adults with bronchiectasis. Any underlying disorder (immunodeficiency, aspiration) that may be contributing must be addressed. When localized bronchiectasis becomes more severe or resistant to medical management, segmental or lobar resection may be warranted. Lung transplantation can also be performed in patients with bronchiectasis. A review of randomized trials among adult patients with bronchiectasis did not find strong evidence to support the routine use of inhaled corticosteroids, although some studies demonstrate improved quality of life and reduced exacerbations in patients with bronchiectasis treated with inhaled corticosteroids. Although preventative strategies, including immunization against typical respiratory pathogens (influenza, pneumococci), are generally recommended, no studies have been conducted to date to address the efficacy of these recommendations.

PROGNOSIS
Children with bronchiectasis often suffer from recurrent pulmonary illnesses, resulting in missed school days, stunted growth, osteopenia, and osteoporosis. The prognosis for patients with bronchiectasis has improved considerably in the past few decades. Earlier recognition or prevention of predisposing conditions, more powerful and broad-spectrum antibiotics, and improved surgical outcomes are likely reasons.

*Bibliography is available at Expert Consult.*
Bibliography
Chapter 402
Pulmonary Abscess
Oren J. Lakser

Lung infection that destroys the lung parenchyma, resulting in cavitations and central necrosis, can result in localized areas composed of thick-walled purulent material, called lung abscesses. Primary lung abscesses occur in previously healthy patients with no underlying medical disorders and are usually solitary. Secondary lung abscesses occur in patients with underlying or predisposing conditions and may be multiple. Lung abscesses are much less common in children (estimated at 0.7 per 100,000 admissions per year) than in adults.

**PATHOLOGY AND PATHOGENESIS**

A number of conditions predispose children to the development of pulmonary abscesses, including aspiration, pneumonia, cystic fibrosis (see Chapter 403), gastroesophageal reflux (see Chapter 323), tracheoesophageal fistula (see Chapter 319), immunodeficiencies, postoperative complications of tonsillectomy and adenoidectomy, seizures, a variety of neurologic diseases, and other conditions associated with impaired mucociliary defense. In children, aspiration of infected materials or a foreign body is the predominant source of the organisms causing abscesses. Initially, pneumonitis impairs drainage of fluid or the aspirated material. Inflammatory vascular obstruction occurs, leading to tissue necrosis, liquefaction, and abscess formation. Abscess can also occur as a result of pneumonia and hematogenous seeding from another site.

If the aspiration event occurred while the child was recumbent, the right and left upper lobes and apical segment of the right lower lobes are the dependent areas most likely to be affected. In a child who was upright, the posterior segments of the upper lobes were dependent and therefore are most likely to be affected. Primary abscesses are found most often on the right side, whereas secondary lung abscesses, particularly in immunocompromised patients, have a predilection for the left side.

Both anaerobic and aerobic organisms can cause lung abscesses. Common anaerobic bacteria that can cause a pulmonary abscess include *Bacteroides* spp., *Fusobacterium* spp., and *Peptostreptococcus* spp. Abscesses can be caused by aerobic organisms such as *Streptococcus* spp., *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and very rarely *Mycoplasma pneumoniae*. Aerobic and anaerobic cultures should be part of the work-up for all patients with lung abscess. Occasionally, concomitant viral–bacterial infection can be detected. Fungi can also cause lung abscesses, particularly in immunocompromised patients.

**CLINICAL MANIFESTATIONS**

The most common symptoms of pulmonary abscess in the pediatric population are cough, fever, tachypnea, dyspnea, chest pain, vomiting, sputum production, weight loss, and hemoptysis. Physical examination typically reveals tachypnea, dyspnea, retractions with accessory muscle use, decreased breath sounds, and dullness to percussion in the affected area. Crackles and, occasionally, a prolonged expiratory phase may be heard on lung examination.

**DIAGNOSIS**

Diagnosis is most commonly made on the basis of chest radiography. Classically, the chest radiograph shows a parenchymal inflammation with a cavity containing an air–fluid level (Fig. 402-1). A chest CT scan can provide better anatomic definition of an abscess, including location and size (Fig. 402-2).

An abscess is usually a thick-walled lesion with a low-density center progressing to an air–fluid level. Abscesses should be distinguished from pneumatoceles, which often complicate severe bacterial pneumonias and are characterized by thin- and smooth-walled, localized air collections with or without air–fluid level (Fig. 402-3). Pneumatoceles often resolve spontaneously with the treatment of the specific cause of the pneumonia.

The determination of the etiologic bacteria in a lung abscess can be very helpful in guiding antibiotic choice. Although Gram stain of sputum can provide an early clue as to the class of bacteria involved, sputum cultures typically yield mixed bacteria, and therefore are not always reliable. Attempts to avoid contamination from oral flora include direct lung puncture, percutaneous (aided by CT guidance) or transtracheal aspiration, and bronchoalveolar lavage specimens obtained bronchoscopically. Bronchoscopic aspiration should be avoided as it can be complicated by massive intrabronchial aspiration, and great care should therefore be taken during the procedure. To avoid invasive procedures in previously normal hosts, empiric therapy can be initiated in the absence of culturable material.
techniques, often with CT guidance, are the initial and, often, only intervention required. Thorascopic drainage has also been successfully utilized with minimal complications. In rare complicated cases, thora
cotomy with surgical drainage or lobectomy and/or decortication may be necessary.

PROGNOSIS
Overall, prognosis for children with primary pulmonary abscesses is excellent. The presence of aerobic organisms may be a negative prog
nostic indicator, particularly in those with secondary lung abscesses. Most children become asymptomatic within 7-10 days, although the fever can persist for as long as 3 wk. Radiologic abnormalities usually resolve in 1-3 mo but can persist for years.

Bibliography is available at Expert Consult.
Bibliography
Figure 402-3 Appearance over a period of 5 days of a large multiloculated pneumonocele in a segment of alveolar consolidation. A, There is a large cavity with 2 air–fluid levels in a segment of alveolar pneumonia in the right upper lobe. B, Five days later, the cavity and most of the pneumonic consolidation have disappeared. (From Silverman FN, Kuhn JP: Essentials of Caffey’s pediatric x-ray diagnosis, Chicago, 1990, Year Book, p. 303.)
Cystic fibrosis (CF) is an inherited multisystem disorder of children and adults; it is the most common life-limiting recessive genetic trait among whites. Dysfunction of the cystic fibrosis transmembrane conductance regulator protein (CFTR), the primary defect, leads to a wide and variable array of presenting manifestations and complications. CF is responsible for most cases of exocrine pancreatic insufficiency in early life and is the major cause of severe chronic lung disease in children. It is also responsible for many cases of hyponatremic salt depletion, nasal polyposis, pansinusitis, rectal prolapse, pancreatitis, cholelithiasis, and nonautoimmune insulin-dependent hyperglycemia. Because CF may manifest as failure to thrive and, occasionally, as cirrhosis or other forms of hepatic dysfunction, this disorder enters into the differential diagnosis of many pediatric conditions (Table 403-1).

**GENETICS**

CF occurs most frequently in white populations of northern Europe, North America, and Australia/New Zealand. The prevalence in these populations varies but approximates 1 in 3,500 live births (1 in 9,200 individuals of Hispanic descent and 1 in 15,000 African-Americans). Although less frequent in African, Hispanic, Middle Eastern, South Asian, and eastern Asian populations, the disorder does exist in these populations as well (Fig. 403-1).

CF is inherited as an autosomal recessive trait. The CF gene codes for the CFTR protein, which is 1,480 amino acids long. CFTR is expressed largely in epithelial cells of airways, the gastrointestinal tract (including the pancreas and biliary system), the sweat glands, and the genitourinary system. CFTR is a member of the adenosine triphosphate–binding cassette superfamily of proteins. It functions as a chloride channel and has other regulatory functions that are perturbed variably by the different mutations. More than 1,900 CFTR polymorphisms grouped into 5 main classes of mutations that affect protein function are associated with the CF syndrome (Table 403-2). The most prevalent mutation of CFTR is the deletion of a single phenylalanine residue at amino acid 508 (F508del). This mutation is responsible for the high incidence of CF in northern European populations and is considerably less frequent in other populations, such as those of southern Europe and Israel. Approximately 50% of individuals with CF who are of northern European ancestry are homozygous for F508del, and more than 80% carry at least 1 F508del gene. Remaining patients have an extensive array of mutations, none of which has a prevalence of more than several percentage points, except in certain populations; for example, the W1282X mutation occurs in 60% of Ashkenazi Jews with CF.

The relationship between CFTR genotype and clinical phenotype is...
Cystic Fibrosis

**Approximate cystic fibrosis birth prevalence and common mutations for selected countries.** Birth prevalence is reported as number of live births per case of cystic fibrosis. Common/important mutations in each region are listed below the prevalence figures. The birth prevalence can vary greatly among ethnic groups in a country. *(From O’Sullivan BP, Freedman SD: Cystic fibrosis, Lancet 373:1891–1902, 2009.)*

![Image of a map showing cystic fibrosis birth prevalence and common mutations for selected countries.](image)

**Table 403-2 One Proposed Classification of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutations**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>EFFECT ON CFTR</th>
<th>FUNCTIONAL CFTR PRESENT?</th>
<th>SAMPLE MUTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Lack of protein production</td>
<td>No</td>
<td>Stop codons (designation in X, e.g., Trp1282X, Gly542X); splicing defects with no protein production (e.g., 711+1G→T, 1717-1G→A)</td>
</tr>
<tr>
<td>II</td>
<td>Defect in protein trafficking with ubiquitination and degradation in endoplasmic reticulum/Golgi body</td>
<td>No/substantially reduced</td>
<td>Phe508del, Asn1303Lys, Gly542X, Arg117His</td>
</tr>
<tr>
<td>III</td>
<td>Defective regulation; CFTR not activated by adenosine triphosphate or cyclic adenosine monophosphate</td>
<td>No (nonfunction CFTR present in apical membrane)</td>
<td>Gly551Asp, Ser492Phe, Val520Glu, Arg553Gly, Arg560Thr, Arg560Ser</td>
</tr>
<tr>
<td>IV</td>
<td>Reduced chloride transport through CFTR at the apical membrane</td>
<td>Yes</td>
<td>Ala455Glu, Arg117Cys, Asp1152His, Arg117His*</td>
</tr>
<tr>
<td>V</td>
<td>Splicing defect with reduced production of CFTR</td>
<td>Yes</td>
<td>3849+10kbC→T, 1811+16kbA→G, IVS8-5G→A</td>
</tr>
</tbody>
</table>

*Function of Arg117His depends on the length of the polythymidine track on the same chromosome in intron 8 (IVS8): 5T, 7T, or 9T. There is more normal CFTR function with a longer polythymidine track. *(From O’Sullivan BP, Freedman SD: Cystic fibrosis, Lancet 373:1891–1902, 2009.)*

highly complex and is not predictable for individual patients. Mutations categorized as "severe" are associated almost uniformly with pancreatic insufficiency but only in general with more rapid progression of lung disease. A few mutations, such as 3849+10kbC→T, are found in patients with normal sweat chloride concentrations. Some individuals with polymorphisms of both CFTR genes have few or no CF manifestations until adolescence or adulthood, when they present with pancreatitis, sinusitis, diffuse bronchiectasis, or male infertility. Whereas *CFTR* mutations are a sine qua non for CF, 2 mutations of *CFTR* can cause disorders that do not meet diagnostic criteria for CF and, occasionally, do not cause discernible clinical problems. Non-CFTR modifier gene polymorphisms appear to be responsible for
much of the variation in the progression of lung disease. Genomewide association studies provide an unbiased approach to test for novel polymorphisms that associate with CF lung disease severity. Genomewide association studies identified a polymorphism on chromosome 11 in the intergenic region between EHF (an epithelial transcription factor) and APIP (an inhibitor of apoptosis) that is associated with lung disease severity, and may influence the expression of EHF and APIP as well as other genes in the region, including PDHX, CD44, and ELFS. A region on chromosome 20 was also found to relate to lung disease severity. This region encompasses several genes (MC3R, CASS4, AURKA) that may play a role in lung host-defense involving neutrophil function, apoptosis, and phagocytosis. Genomewide association studies analysis also identified genetic regions that predispose to risk for liver disease, CF-related diabetes, and meconium ileus.

Through the use of probes for 40 of the most common mutations, the genotype of 80-90% of Americans with CF can be ascertained. Genotyping using a discreet panel of mutation probes is quick and less costly than more comprehensive sequencing and is commercially available. In special cases, sequencing the entire CF gene is necessary to establish the genotype. This procedure is also available commercially and can identify polymorphisms and unique mutations of unknown clinical importance.

The high frequency of CFTR mutations has been ascribed to resistance to the morbidity and mortality associated with infectious diseases through the ages. In support of this hypothesis, cultured CF intestinal epithelial cells homozygous for the F508del mutation are unresponsive to the secretory effects of cholera toxin. CFTR heterozygous mice experience less mortality when treated with cholera toxin than their unaffected wild type littermates.

### PATHOGENESIS

A number of long-standing observations of CF are of fundamental pathophysiologic importance; they include failure to clear mucous secretions, a paucity of water in mucous secretions, an elevated salt content of sweat and other serous secretions, and chronic infection limited to the respiratory tract. Additionally, there is a greater negative potential difference across the respiratory epithelia of patients with CF than across the respiratory epithelia of control subjects. Aberrant electrical properties are also demonstrated for CF sweat gland duct and rectal epithelia. The membranes of CF epithelial cells are unable to secrete chloride ions in response to cyclic adenosine monophosphate-mediated signals, and at least in the respiratory tract, excessive amounts of sodium are absorbed through these membranes (Fig. 403-2). These defects can be traced to a dysfunction of CFTR (Figs. 403-3 and 403-4).

Cyclic adenosine monophosphate–stimulated protein kinase A regulation of chloride conductance is the primary function of CFTR; this function is absent in epithelial cells with many different mutations of the CFTR gene. CFTR mutations fall into 5 classes in another classification system, albeit with some overlap (see Fig. 403-4). Individuals with classes I, II, and III mutations, on average, have shorter survival than those with “mild” genotypes (class IV or V). The clinical importance of these functional categories is limited because they do not uniformly correlate with specific clinical features or their severity. Rather, clinical features correlate with the residual CFTR activity.

Many hypotheses have been postulated to explain how CFTR dysfunction results in the clinical phenotype. It is likely that no one hypothesis explains the full spectrum of disease. Most believe that the epithelial pathophysiologic in airways involves an inability to secrete salt and secondarily to secrete water in the presence of excessive reabsorption of salt and water. The proposed outcome is insufficient water on the airway surface to hydrate secretions. Desiccated secretions become more viscous and elastic (rubbery) and are harder to clear by mucociliary and other mechanisms. In addition it has been suggested that CFTR dysfunction results in an altered microenvironment with low HCO3− and a more acidic pH, thus altering mucus rheology and aggravating poor mucociliary clearance. The result is that these secretions are retained and obstruct airways, starting with those of the smallest caliber, the bronchioles. Airflow obstruction at the level of small airways is the earliest observable physiologic abnormality of the respiratory system.

It is plausible that similar pathophysiologic events take place in the pancreatic and biliary ducts (and in the vas deferens), leading to desiccation of proteinaceous secretions and obstruction. Because the function of sweat gland duct cells is to absorb rather than secrete chloride, salt is not retrieved from the isotonic primary sweat as it is transported to the skin surface; chloride and sodium levels are consequently elevated.

Chronic infection in CF is limited to the airways. A likely explanation for infection is a sequence of events starting with failure to clear inhaled bacteria promptly and then proceeding to persistent colonization and an inflammatory response in airway walls. In addition, it has

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**Figure 403-2** The net ion flow across normal and cystic fibrosis (CF) airway epithelia under basal conditions (large arrows). Because water follows salt movement, the predicted net flux of water would be from the airway lumen to the submucosa and would be greater across CF epithelia. The increased Na+ absorption by CF cells is associated with an increased amiloride-sensitive Na+ conductance across the apical (luminal) membrane and increased Na+,K+-adenosine triphosphatase (ATPase) sites at the basolateral membrane. The cyclic adenosine monophosphate (cAMP)–mediated apical membrane conductance of Cl− associated with the CF transmembrane regulator (CFTR) does not function in CF epithelia, but an alternative, calcium (Ca++)–activated Cl− conductance is present in normal and CF cells. It is postulated that CF cells have a limited ability to secrete Cl− and absorb Na+ in excessive amounts, limiting the water available to hydrate secretions and allow them to be cleared from the airways lumen. Cl−, Ca++–activated Cl− conductance: Cl−CFTR, the CFTR Cl− channel. (From Knowles MR: Contemporary perspectives on the pathogenesis of cystic fibrosis, New Insights Cystic Fibrosis 1:1, 1993.)
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provides a hypoxic environment and thereby protects Pseudomonas against antimicrobial agents. Nutritional deficits, including fatty acid deficiency, have been implicated as predisposing factors for respiratory tract infection. More specifically, concentrations of lipoxins—molecules that suppress neutrophilic inflammation—are suppressed in CF airways. Supporting this idea is the observation that the 10-15% of individuals with CF who retain substantial exocrine pancreatic function have delayed onset of respiratory disease.

Figure 403-3 Hypothesized structure of cystic fibrosis transmembrane regulator (CFTR). The protein contains 1,480 amino acids and a number of discrete globular and transmembrane domains. Activation of CFTR relies on phosphorylation, particularly through protein kinase A but probably involving other kinases as well. Channel activity is governed by the 2 nucleotide-binding domains, which regulate channel gating. The carboxyl terminal (consisting of threonine, arginine, and leucine [TRL]) of CFTR is anchored through a PDZ-type binding interaction with the cytoskeleton and is kept in close approximation (dashed lines) to a number of important proteins. These associated proteins influence CFTR functions, including conductance, regulation of other channels, signal transduction, and localization at the apical plasma membrane. Each membrane-spanning domain contains 6 membrane-spanning α helices, portions of which form a chloride-conductance pore. The regulatory domain is a site of protein kinase A phosphorylation. The common F508del mutation occurs on the surface of nucleotide-binding domain 1. (From Rowe SM, Miller S, Sorscher EJ: Cystic fibrosis, N Engl J Med 352:1992–2001, 2005.)

been proposed that abnormal CFTR creates a proinflammatory state or amplifies the inflammatory response to initial infections (viral or bacterial). Some investigators have identified primary differences in CF-affected immune cells and have suggested that these alterations contribute to this proinflammatory state. It appears that inflammatory events occur first in small airways, perhaps because clearance of altered secretions and microorganisms from these regions is more difficult. Chronic bronchiolitis and bronchitis are the initial lung manifestations (see Chapter 391), but after months to years, structural changes in airway walls produce bronchiolectasis and bronchiectasis. The agents of airway injury include neutrophil products, such as oxidative radicals and proteases, and immune reaction products. With advanced lung disease, infection may extend to peribronchial lung parenchyma.

A finding that is not readily explained by CFTR dysfunction is the high prevalence in patients with CF of CF airway colonization with Staphylococcus aureus (see Chapter 181.1), Pseudomonas aeruginosa (see Chapter 205.1), and Burkholderia cepacia complex (see Chapter 205.2), organisms that rarely infect the lungs of other individuals. It has been postulated that the CF airway epithelial cells or surface liquids may provide a favorable environment for harboring these organisms. CF airway epithelium may be compromised in its innate defenses against these organisms, through either acquired or genetic alterations. Antimicrobial activity is diminished in CF secretions; this diminution may be related to hyperacidic surface liquids or other effects on innate immunity. Another puzzle is the propensity for P. aeruginosa to undergo mucoid transformation in the CF airways. The complex polysaccharide produced by these organisms generates a biofilm that provides a hypoxic environment and thereby protects Pseudomonas against antimicrobial agents.

Nutritional deficits, including fatty acid deficiency, have been implicated as predisposing factors for respiratory tract infection. More specifically, concentrations of lipoxins—molecules that suppress neutrophilic inflammation—are suppressed in CF airways. Supporting this idea is the observation that the 10-15% of individuals with CF who retain substantial exocrine pancreatic function have delayed onset of respiratory disease.

Figure 403-4 Classes of CFTR (cystic fibrosis transmembrane regulator) mutations. Classes of defects in the CFTR gene include the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered regulation, such as diminished adenosine triphosphate (ATP) binding and hydrolysis (class III); defective chloride conductance or channel gating (class IV); and a reduced number of CFTR transcripts due to a promoter or splicing abnormality (class V). (Copyright Michael Linkinhoker, Link Studio.)
colonization with *P. aeruginosa* and slower deterioration of lung function. It appears that nutritional factors are only contributory because preservation of pancreatic function does not preclude development of typical lung disease.

**PATHOLOGY**

The earliest pathologic lesion in the lung is that of bronchiolitis (mucous plugging and an inflammatory response in the walls of the small airways); with time, mucus accumulation and inflammation extend to the larger airways (bronchitis) (see Chapter 391). Goblet cell hyperplasia and submucosal gland hypertrophy become prominent pathologic findings, which is most likely a response to chronic airway infection. Organs appear to be confined to the endobronchial space; invasive bacterial infection is not characteristic. With longstanding disease, evidence of airway destruction such as bronchiolar obliteration, bronchiolectasis, and bronchiectasis (see Chapter 401) becomes prominent. Imaging modalities demonstrate both increased airway wall thickness and luminal cross-sectional area relatively early in lung disease evaluation. Bronchiectatic cysts and emphysematous bullae or subpleural blebs are frequent with advanced lung disease, the upper lobes being most commonly involved. These enlarged air spaces may rupture and cause pneumothorax. Interstitial disease is not a prominent feature, although areas of fibrosis appear eventually. Bronchial arteries are enlarged and tortuous, contributing to a propensity for hemoptysis in bronchiectatic airways. Small pulmonary arteries eventually display medial hypertrophy, which would be expected in secondary pulmonary hypertension.

The paranasal sinuses are uniformly filled with secretions containing inflammatory products, and the epithelial lining displays hyperplastic and hypertrophied secretory elements (see Chapter 380). Polypoid lesions within the sinuses and erosion of bone have been reported. The nasal mucosa may form large or multiple polyps, usually from a base surrounding the ostia of the maxillary and ethmoidal sinuses.

The pancreas is usually small, occasionally cystic, and often difficult to find at postmortem examination. The extent of involvement varies at birth. In infants, the acini and ducts are often distended and filled with eosinophilic material. In 85-90% of patients, the lesion progresses to complete or almost complete disruption of acini and replacement with fibrous tissue and fat. Infrequently, foci of calcification may be seen on radiographs of the abdomen. The islets of Langerhans contain normal-appearing β cells, although they may begin to show architectural disruption by fibrous tissue in the 2nd decade of life.

The intestinal tract shows only minimal changes. Esophageal and duodenal glands are often distended with mucous secretions. Concretions may form in the appendiceal lumen or cecum. Crypts of the appendix and rectum may be dilated and filled with secretions.

**Focal biliary cirrhosis** secondary to blockage of intrahepatic bile ducts is uncommon in early life, although it is responsible for occasional cases of prolonged neonatal jaundice. This lesion becomes much more prevalent and extensive with age and is found in 70% of patients at postmortem examination. This process can proceed to symptomatic multilobular biliary cirrhosis that has a distinctive pattern of large irregular parenchymal nodules and interspersed bands of fibrous tissue. Approximately 30-70% of patients have fatty infiltration of the liver, in some cases despite apparently adequate nutrition. At autopsy, hepatic congestion secondary to cor pulmonale is frequently observed. The gallbladder may be hypoplastic and filled with mucoid material and often contains stones. The epithelial lining often displays extensive mucous metaplasia. Atresia of the cystic duct and stenosis of the distal common bile duct have been observed.

Glands of the uterine cervix are distended with mucus, copious amounts of which collect in the cervical canal. In >95% of males, the body and tail of the epididymis, the vas deferens, and the seminal vesicles are obliterated or atretic, resulting in male infertility.

**CLINICAL MANIFESTATIONS**

Mutational heterogeneity and environmental factors appear responsible for highly variable involvement of the lungs, pancreas, and other organs. A list of presenting manifestations is lengthy, although pulmonary and gastrointestinal presentations predominate (Fig. 403-5). With inclusion of CF newborn screening panels, an increasing proportion of children are diagnosed before symptoms appear.

**Respiratory Tract**

Cough is the most constant symptom of pulmonary involvement. At first, the cough may be dry and hacking, but eventually it becomes loose and productive. In older patients, the cough is most prominent upon arising in the morning or after activity. Expectorated mucus is usually purulent. Some patients remain asymptomatic for long periods or seem to have prolonged but intermittent acute respiratory infections. Others acquire a chronic cough in the 1st few wk of life, or they

![Figure 403-5 Approximate age of onset of clinical manifestations of cystic fibrosis. ABPA, allergic bronchopulmonary aspergillosis; CBAVD, congenital bilateral absence of the vas deferens; CF, cystic fibrosis; DIOS, distal intestinal obstruction syndrome; HPOA, hypertrophic pulmonary osteoarthropathy. (From O’Sullivan BP, Freedman SD: Cystic fibrosis, Lancet 373:1891–1902, 2009.)](image-url)
have pneumonia repeatedly. Extensive bronchiolitis accompanied by wheezing is a frequent symptom during the 1st few yr of life. As lung disease slowly progresses, exercise intolerance, shortness of breath, and failure to gain weight or grow are noted. Exacerbations of lung symptoms, presumably owing to more active airways infection, often require repeated hospitalizations for effective treatment. Cor pulmonale, respiratory failure, and death eventually supervene unless lung transplantation is accomplished. Colonization with B. cepacia and other multidrug-resistant organisms may be associated with particularly rapid pulmonary deterioration and death.

The rate of progression of lung disease is the chief determinant of morbidity and mortality. The course of lung disease is largely independent of genotype. Male gender and exocrine pancreatic sufficiency are also associated with a slower rate of pulmonary function decline.

Early physical findings include increased anteroposterior diameter of the chest, generalized hyperresonance, scattered or localized coarse crackles, and digital clubbing. Expiratory wheezes may be heard, especially in young children. Cyanosis is a late sign. Common pulmonary complications include atelectasis, hemoptysis, pneumothorax, and cor pulmonale; these usually appear beyond the 1st decade of life.

Even though the paranasal sinuses are virtually always opacified radiographically, acute sinusitis is infrequent. Nasal obstruction and rhinorrhea are common, caused by inflamed, swollen mucous membranes or, in some cases, nasal polyps. Nasal polyps are most troublesome between 5 and 20 yr of age.

**Intestinal Tract**

In 10-15% of newborn infants with CF, the ileum is completely obstructed by meconium (meconium ileus). The frequency is greater (=30%) among siblings born subsequent to a child with meconium ileus and is particularly striking in monozygotic twins, reflecting a genetic contribution from 1 or more modifying genes. Abdominal distention, emesis, and failure to pass meconium appear in the 1st 24-48 hr of life (see Chapters 102.1 and 330.2). Abdominal radiographs (Fig. 403-6) show dilated loops of bowel with air–fluid levels and, frequently, a collection of granular, “ground-glass” material in the lower central abdomen. Rarely, meconium peritonitis results from intrauterine rupture of the bowel wall and can be detected radiographically as the presence of peritoneal or scrotal calcifications. Meconium plug syndrome occurs with increased frequency in infants with CF but is less specific than meconium ileus. Ileal obstruction with fecal material (distal intestinal obstruction syndrome) occurs in older patients, causing cramming abdominal pain and abdominal distention.

More than 85% of affected children show evidence of protein and fat malabsorption from exocrine pancreatic insufficiency. Symptoms include frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large. Characteristically, stools contain readily visible droplets of fat. A protuberant abdomen, decreased muscle mass, poor growth, and delayed maturation are typical physical signs. Excessive flatus may be a problem. A number of mutations are associated with preservation of some exocrine pancreatic function, including R117H and 3849 + 10kbC→T. Virtually all individuals homozygous for F508del have pancreatic insufficiency.

Less-common gastrointestinal manifestations include intussusception, fecal impaction of the cecum with an asymptomatic right lower quadrant mass, and epigastric pain owing to duodenal inflammation. Acid or bile reflux with esophagitis symptoms is common in older children and adults. Subacute appendicitis and periappendiceal abscess have been encountered. Historically a relatively common event, rectal prolapse occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy. Occasionally, hypoproteinemia with anasarca appears in malnourished infants, especially if children are fed soy-based preparations. Neurologic dysfunction (dementia, peripheral neuropathy) and hemolytic anemia may occur because of vitamin E deficiency. Deficiency of other fat-soluble vitamins is occasionally symptomatic. Hypoprothrombinemia caused by vitamin K deficiency may result in a bleeding diathesis. Clinical manifestations of other fat-soluble vitamin deficiencies, such as decreased bone density and night blindness, have been noted. Rickets is rare.

**Biliary Tract**

Evidence for liver dysfunction is most often detected in the 1st 15 yr of life and can be found in up to 30% of individuals. Biliary cirrhosis becomes symptomatic in only 5-7% of patients. Manifestations can include icterus, ascites, hematemesis from esophageal varices, and evidence of hypersplenism. A neonatal hepatitis-like picture and massive hepatomegaly owing to steatosis have been reported. Biliary colic secondary to cholelithiasis may occur in the 2nd decade or later. Liver disease occurs independent of genotype but is associated with meconium ileus and pancreatic insufficiency.

**Figure 403-6** A and B, Contrast enema study in a newborn infant with abdominal distention and failure to pass meconium. Notice the small diameter of the sigmoid and ascending colon and dilated, air-filled loops of small intestine. Several air–fluid levels in the small bowel are visible on the upright lateral view.
Cystic Fibrosis–Related Diabetes and Pancreatitis

In addition to exocrine pancreatic insufficiency, evidence for hyperglycemia and glucosuria, including polyuria and weight loss, may appear, especially in the 2nd decade of life. Ketoacidosis usually does not occur, but eye, kidney, and other vascular complications have been noted in patients living ≥10 yr after the onset of hyperglycemia. Recurrent, acute pancreatitis occurs occasionally in individuals who have residual exocrine pancreatic function and may be the sole manifestation of 2 CFTR mutations.

Genitourinary Tract

Sexual development is often delayed but only by an average of 2 yr. More than 95% of males are azoospermic because of failure of development of wolffian duct structures, but sexual function is generally unimpaired. The incidence of inguinal hernia, hydrocele, and undescended testis is higher than expected. Adolescent females may experience secondary amenorrhea, especially with exacerbations of pulmonary disease. The female fertility rate is diminished. Pregnancy is generally tolerated well by women with good pulmonary function but may accelerate pulmonary progression in those with moderate or advanced lung problems. Urinary incontinence associated with cough occurs in 18-47% of female children and adolescents.

Sweat Glands

Excessive loss of salt in the sweat predisposes young children to salt depletion episodes, especially during episodes of gastroenteritis and during warm weather. These children present with hypochloremic alkalosis. Hyponatremia is a risk particularly in warm climates. Frequently, parents notice salt "frosting" of the skin or a salty taste when they kiss the child. A few genotypes are associated with normal sweat chloride values.

DIAGNOSIS AND ASSESSMENT

The diagnosis of CF has been based on a positive quantitative sweat test (CF: ≥60 mEq/L) in conjunction with 1 or more of the following features: typical chronic obstructive pulmonary disease, documented exocrine pancreatic insufficiency, and a positive family history. With newborn screening, diagnosis is often made prior to obvious clinical manifestations such as failure to thrive and chronic cough. Diagnostic criteria have been recommended to include additional testing procedures (Table 403-3).

Sweat Testing

The sweat test, which involves using pilocarpine iontophoresis to collect sweat and performing chemical analysis of its chloride content, is the standard approach to diagnosis of CF. The procedure requires care and accuracy. An electric current is used to carry pilocarpine into the skin of the forearm and locally stimulate the sweat glands. If an adequate amount of sweat is collected, the specimens are analyzed for chloride concentration. Testing may be difficult in the 1st 2 wk of life because of low sweat rates but is recommended any time after the 1st 48 hr of life. Positive results should be confirmed; for a negative result, the test should be repeated if suspicion of the diagnosis remains.

More than 60 mEq/L of chloride in sweat is diagnostic of CF when 1 or more other criteria are present. Threshold levels of 30-40 mEq/L for infants have been suggested. Borderline (or intermediate) values of 40-60 mEq/L have been reported in patients of all ages who have CF with atypical involvement and require further testing. Chloride concentrations in sweat are somewhat lower in individuals who retain exocrine pancreatic function but usually remain within the diagnostic range. Table 403-4 lists the conditions associated with false-negative and false-positive sweat test results.

DNA Testing

Several commercial laboratories test for 30-96 of the most common CFTR mutations. This testing identifies ≥90% of individuals who carry 2 CF mutations. Some children with typical CF manifestations are found to have 1 or no detectable mutations by this methodology. Some laboratories perform comprehensive mutation analysis screening for all of the >1,900 identified mutations.

Other Diagnostic Tests

The finding of increased potential differences across nasal epithelium (nasal potential difference) that is the increased voltage response to topical amiloride application, followed by the absence of a voltage response to a β-adrenergic agonist, has been used to confirm the diagnosis of CF in patients with equivocal or frankly normal sweat chloride values.

Pancreatic Function

Exocrine pancreatic dysfunction is clinically apparent in many patients. Documentation is desirable if there are questions about the functional status of the pancreas. The diagnosis of pancreatic malabsorption can be made by the quantification of elastase-1 activity in a fresh stool sample by an enzyme-linked immunosorbent assay specific for human elastase. To determine the degree of fat malabsorption, a 72 hr stool

<table>
<thead>
<tr>
<th>Table 403-4</th>
<th>Conditions Associated with False-Positive and False-Negative Sweat Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WITH FALSE-POSITIVE RESULTS</strong></td>
<td>Eczema (atopic dermatitis)</td>
</tr>
<tr>
<td><strong>WITH FALSE-NEGATIVE RESULTS</strong></td>
<td>Dilution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 403-3</th>
<th>Diagnostic Criteria for Cystic Fibrosis (CF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)</td>
<td>A history of CF in a sibling</td>
</tr>
</tbody>
</table>
collection is performed for total fat quantitation with a simultaneous diet history to determine a coefficient of fat absorption. Normal fat absorption is greater than 93% of fat ingestion. Endocrine pancreatic dysfunction may be more prevalent than previously recognized. Cystic fibrosis–related diabetes affects approximately 19% of adolescents and 40-50% of adults. Many authorities advocate yearly monitoring with a modified 2 hr oral glucose tolerance test after 10 yr of age. This approach is more sensitive than spot checks of blood and urine glucose levels and glycosylated hemoglobin levels.

**Radiology**

Pulmonary radiologic findings suggest the diagnosis but are not specific. Hyperinflation of lungs occurs early and may be overlooked in the absence of infiltrates or streaky densities. Bronchial thickening and plugging and ring shadows suggesting bronchiectasis usually appear first in the upper lobes. Nodular densities, patchy atelectasis, and confluent infiltrate follow. Hilar lymph nodes may be prominent. With advanced disease, impressive hyperinflation with markedly depressed diaphragms, anterior bowing of the sternum, and a narrow cardiac shadow are noted. Cyst formation, extensive bronchiectasis, dilated pulmonary artery segments, and segmental or lobar atelectasis is often apparent with advanced disease. Figure 403-7 shows typical progression of lung disease. Most CF centers obtain chest radiographs (posteroanterior [PA] and lateral) at least annually. Standardized scoring of roentgenographic changes has been used to follow progression of lung disease. CT of the chest can detect and localize thickening of bronchial airway walls, mucous plugging, focal hyperinflation, and early bronchiectasis (Fig. 403-8); it is generally not used for routine evaluation of chest disease. Many children with normal lung function have bronchiectasis on CT, indicating that this imaging modality is sensitive to early lung changes.

Radiographs of paranasal sinuses reveal panopacification and, often, failure of frontal sinus development. CT provides better resolution of sinus changes if this information is required clinically. Fetal ultrasonography may suggest ileal obstruction with meconium early in the 2nd trimester, but this finding is not predictive of meconium ileus at birth.

**Pulmonary Function**

Standard pulmonary function studies are not obtained until patients are 4-6 yr of age, by which time many patients show the typical pattern of obstructive pulmonary involvement (see Chapter 384). Decrease in the midmaximal flow rate is an early functional change, reflecting small airway obstruction. This lesion also affects the distribution of

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Figure 403-7 Serial radiographs in a boy show the changing appearance of cystic fibrosis over 6 yr. A, At 9 yr, frontal radiograph shows minimal peribronchial thickening and hyperaerated lungs indistinguishable from asthma. B, Nineteen months later, the radiographic picture has worsened considerably. Extensive peribronchial thickening is now noted. Mucoid impaction of the bronchus is seen in the left upper lobe and hilar shadows have become abnormally prominent. C, Ten months later, further deterioration is obvious. Widespread typical changes of CF are noted throughout both lungs. D, Follow-up studies show considerable improvement, which suggested that some of the changes evident on C were from superimposed infection. E, One year later, note the progressive changes of CF—most severe in the upper lobes bilaterally. (From Long FR, Druhan SM, Kuhn JP. Diseases of the bronchi and pulmonary aeration. In Slovis TL, editor, Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 73-54.)
ventilation and increases the alveolar-arterial oxygen difference. The findings of obstructive airway disease and modest responses to a bronchodilator are consistent with the diagnosis of CF at all ages. Residual volume and functional residual capacity are increased early in the course of lung disease. Restrictive changes, characterized by declining total lung capacity and vital capacity, correlate with extensive lung injury and fibrosis and are a late finding. Testing at each clinic visit is recommended to evaluate the course of the pulmonary involvement and allow for early intervention when substantial decrements are documented. Increasing numbers of CF centers are equipped to measure airflow patterns of sedated infants (infant pulmonary function tests). Some patients reach adolescent or adult life with normal pulmonary function and without evidence of overinflation.

**Microbiologic Studies**

The finding of *S. aureus* or *P. aeruginosa* on culture of the lower airways (sputum) strongly suggests a diagnosis of CF. In particular, mucoid forms of *P. aeruginosa* are often recovered from CF lungs. *B. cepacia complex* recovery also suggests CF. A wide range of other organisms are frequently recovered, particularly in advanced lung disease; they include a variety of Gram-negative rods including *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*, fungi, and nontuberculous mycobacterial species. Failure of respiratory symptom flares to respond to usual antibiotics triggers testing for *Mycoplasma* and viruses. Fiberoptic bronchoscopy is used to gather lower respiratory tract secretions of infants and young children who do not expectorate.

**Heterozygote Detection and Prenatal Diagnosis**

Mutation analysis should be fully informative for testing of potential carriers or a fetus, provided that mutations within the family have been previously identified. Testing a spouse of a carrier with a standard panel of probes is ≈90% sensitive, and full CFTR sequence analysis is commercially available if further testing is warranted. Prenatal testing should be offered to all couples planning to have children in addition to individuals with a family history of CF and partners of CF women. The American College of Medical Genetics and the American College of Obstetricians and Gynecologists recommend that CF carrier screening be offered to individuals of Ashkenazi Jewish or white descent and be made available to individuals of other ethnic and racial groups; in one large series, 14% of carrier screening referrals were from Hispanic and African-American individuals, and 12% from individuals with ethnicities other than white or Ashkenazi Jewish. Screening of the siblings of an affected child is also suggested.

**Newborn Screening**

Newborn screening for CF is mandated in all 50 states. A variety of newborn screening algorithms are in place to identify infants with CF. Most algorithms utilize a combination of immunoreactive trypsinogen results and limited DNA testing on blood spots; all positive screens are followed by a confirmatory sweat analysis. This screening test is ≈95% sensitive. Newborn diagnoses can prevent early nutritional deficiencies and improve long-term growth and may improve cognitive function. Importantly, good nutritional status (50% weight for height or 50% body mass index) is associated with better lung function at 6 yr of age. There is a subset of infants with a positive newborn screen for CF, elevated *Mycoplasma* and nontuberculous mycobacterial species. Failure of respiratory infection can occur gradually and be seen. A sputum sample or, if that is not available, a lower pharyngeal swab taken during or after a forced cough is obtained for culture and antibiotic susceptibility studies. Because irreversible loss of pulmonary function from low-grade infection can occur gradually and without acute symptoms, emphasis is placed on a thorough pulmonary history. Table 403-5 lists symptoms and signs that suggest the need for more intensive antibiotic and physical therapy. Protection against methicillin-resistant *S. aureus*, *P. aeruginosa*, *B. cepacia*, and other resistant Gram-negative organisms is essential, including isolation procedures and careful attention to sterilization of inhalation therapy equipment. A nurse, physical therapist, respiratory therapist, social worker, and dietitian, as members of the multidisciplinary care team, should evaluate children regularly and contribute to the development of a comprehensive daily care plan. Considerable education and programs to empower families and older children to take responsibility for care are likely to result in the best adherence to daily care programs. Standardization of practice, on the part of both caregivers and families, as well as close monitoring and early intervention for new or increasing symptoms appears to result in the best long-term outcomes.

Because secretions of CF patients are not adequately hydrated, attention in early childhood to oral hydration, especially during warm weather or with acute gastroenteritis, may minimize complications.
associated with impaired mucus clearance. Intravenous therapy for dehydration should be initiated early.

The goal of therapy is to maintain a stable condition for prolonged periods. This can be accomplished for most patients by interval evaluation and adjustments of the home treatment program. Some children have episodic acute or low-grade chronic lung infection that progresses. For these patients, intensive inhalation and airway clearance and intravenous antibiotics are indicated. Improvement is most reliably accomplished in a hospital setting; selected patients have demonstrated successful outcomes while completing these treatments at home. Intravenous antibiotics may be required infrequently or as often as every 2-3 mo. The goal of treatment is to return patients to their previous pulmonary and functional status.

The basic daily care program varies according to the age of the child, the degree of pulmonary involvement, other system involvement, and the time available for therapy. The major components of this care are pulmonary and nutritional therapies. Because therapy is medication-intensive, iatrogenic problems frequently arise. Monitoring for these complications is also an important part of management (Table 403-6).

### Pulmonary Therapy

The object of pulmonary therapy is to clear secretions from airways and to control infection. When a child is not doing well, every potentially useful aspect of therapy should be reconsidered.

#### Inhalation Therapy

Aerosol therapy is used to deliver medications and hydrate the lower respiratory tract. Metered-dose inhalers can deliver some agents, such as bronchodilators and corticosteroids, with a spacer for younger children. Alternately, these medications can be delivered with a compressor that drives a handheld nebulizer. In some patients β-agonists may decrease PaO2 acutely by increasing ventilation-perfusion mismatch, a concern if the PaO2 is marginal.

Human recombinant DNase (2.5 mg), given as a single daily aerosol dose, improves pulmonary function, decreases the number of pulmonary exacerbations, and promotes a sense of well-being in patients who have moderate disease and purulent secretions. Benefit for those with normal forced expiratory volume in 1 sec (FEV1) values or advanced lung disease has also been documented. Improvement is sustained for 12 mo or longer with continuous therapy. Another mucolytic agent, N-acetylcysteine, nebulized as a 5-10% solution following β-agonist nebulization, is useful for airway clearance and may potentially augment airway levels of the antioxidant glutathione.

Nebulized hypertonic saline, acting as a hyperosmolar agent, is believed to draw water into the airway and rehydrate mucus and the periciliary fluid layer, resulting in improved mucociliary clearance. A number of studies have reported that 7% hypertonic saline nebulized 2-4 times daily results in increased mucus clearance and improved pulmonary function.

Aerosolized antibiotics are often used when the airways are colonized with *Pseudomonas* as part of daily therapy. Aerosolized tobramycin, TOBI, or aerosolized aztreonam, Cayston, used as a suppressive therapy (on 1 mo, off 1 mo) may reduce symptoms, improve pulmonary function, and alleviate the need for hospitalization (see "Aerosolized Antibiotic Therapy" below).

#### Airway Clearance Therapy

Airway clearance treatment usually consists of chest percussion combined with postural drainage and derives its rationale from the idea that cough clears mucus from large airways but chest vibrations are required to move secretions from small airways, where expiratory flow rates are low. *Chest physical therapy* (PT) can be particularly useful for patients with CF because they accumulate secretions in small airways first, even before the onset of symptoms. Although immediate improvement of pulmonary function generally cannot be demonstrated after PT, cessation of chest PT in children with mild to moderate airflow limitation results in deterioration of lung function within 3 wk, and prompt improvement of function occurs when therapy is resumed. Chest PT is recommended 1-4 times a day, depending on the severity of lung dysfunction. Cough, huffing, or forced expirations are encouraged after each lung segment is “drained.” Vest-type mechanical percussors are also useful. Voluntary coughing, repeated forced expiratory maneuvers with and without positive expiratory pressure, patterned breathing, and use of an array of handheld oscillatory devices are additional aids to clearance of mucus. Routine aerobic exercise appears to slow the rate of decline of pulmonary function, and benefit has also been documented with weight training. No one airway clearance technique is superior to any other, so all modes should be considered in the development of an airway clearance prescription.

**Table 403-5** Symptoms and Signs Associated with Exacerbation of Pulmonary Infection in Patients with Cystic Fibrosis

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased frequency and duration of cough</td>
</tr>
<tr>
<td>Increased sputum production</td>
</tr>
<tr>
<td>Change in appearance of sputum</td>
</tr>
<tr>
<td>Increased shortness of breath</td>
</tr>
<tr>
<td>Decreased exercise tolerance</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Feeling of increased congestion in the chest</td>
</tr>
</tbody>
</table>

**SIGNS**

- Increased respiratory rate
- Use of accessory muscles for breathing
- Intercostal retractions
- Change in results of auscultatory examination of chest
- Decline in measures of pulmonary function consistent with the presence of obstructive airway disease
- Fever and leukocytosis
- Weight loss
- New infiltrate on chest radiograph


**Table 403-6** Complications of Therapy for Cystic Fibrosis

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>AGENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Corticosteroids (systemic)</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>Corticosteroids (systemic, inhaled)</td>
</tr>
<tr>
<td>Renal dysfunction:</td>
<td></td>
</tr>
<tr>
<td>Tubular</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Semisynthetic penicillins, nonsteroidal antiinflammatory drugs</td>
</tr>
<tr>
<td>Hearing loss, vestibular dysfunction</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Peripheral neuropathy or optic atrophy</td>
<td>Chloramphenicol (prolonged course)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Hyperuricemia, colonic stricture</td>
<td>Pancreatic extracts (very large doses)</td>
</tr>
<tr>
<td>Goiter</td>
<td>Iodine-containing expectorants</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Enamel hypoplasia or staining</td>
<td>Tetracyclines (used in 1st 8 yr of life)</td>
</tr>
</tbody>
</table>

*Common hypersensitivity reactions to drugs are not included.*
Adherence to daily therapy is essential; therefore airway clearance technique plans are individualized for each patient.

**Antibiotic Therapy**

Antibiotics are the mainstay of therapy designed to control progression of lung infection. The goal is to reduce the intensity of endobronchial infection and to delay progressive lung damage. The usual guidelines for acute chest infections, such as fever, tachypnea, or chest pain, are often absent. Consequently, all aspects of the patient’s history and examination, including anorexia, weight loss, and diminished activity, must be used to guide the frequency and duration of therapy. Antibiotic treatment varies from intermittent short courses of 1 antibiotic to nearly continuous treatment with 1 or more antibiotics. Dosages for some antibiotics are often 2-3 times the amount recommended for minor infections because patients with CF have proportionately more lean body mass and higher clearance rates for many antibiotics than other individuals. In addition, it is difficult to achieve effective drug levels of many antimicrobials in respiratory tract secretions.

**Oral Antibiotic Therapy**

Indications for oral antibiotic therapy in a patient with CF include the presence of respiratory tract symptoms and identification of pathogenic organisms in respiratory tract cultures. Whenever possible, the choice of antibiotics should be guided by in vitro sensitivity testing. Common organisms, including S. aureus, nontypeable Haemophilus influenzae, P. aeruginosa; B. cepacia and other Gram-negative rods, are encountered with increasing frequency. The first 2 can be eradicated from the respiratory tract in CF with use of oral antibiotics, but Pseudomonas is more difficult to treat. The usual course of therapy is 2-2 wk, and maximal doses are recommended. Table 403-7 lists useful oral antibiotics. The quinolones are the only broadly effective oral antibiotics for Pseudomonas infection, but resistance against these agents emerges rapidly. Infection with mycoplasma or chlamydial organisms has been documented, providing a rationale for the use of macrolides on an empirical basis for flare of symptoms. Macrolides may reduce the virulence properties of P. aeruginosa, such as biofilm production, and contribute antiinflammatory effects. Long-term therapy with azithromycin 3 times a week improves lung function in patients with chronic P. aeruginosa infection.

**Aerosolized Antibiotic Therapy**

P. aeruginosa and other Gram-negative organisms are frequently resistant to all oral antibiotics. Aerosol delivery of antibiotics has been used as an option for home delivery of additional agents, such as tobramycin, colistin, and gentamicin. Although these therapies are used, the evidence to support aerosolized antibiotics for an acute pulmonary exacerbation is limited. However, there is good evidence to support the use of inhaled tobramycin as a long-term suppressive therapy in a patient colonized with P. aeruginosa. When tobramycin is given at a dose of 300 mg twice daily on alternate months for 6 mo, Pseudomonas density in sputum decreases, fewer hospitalizations are required, and pulmonary function can improve by ≥10%. Toxicity is negligible. On the basis of available evidence, this therapy is recommended in patients with chronic colonization with P. aeruginosa, to lessen symptoms and/or to improve long-term function in patients with moderate to severe disease. Recently, nebulized aztreonam was also approved for 3 times daily therapy on alternate months for patients with chronic P. aeruginosa. Another indication for aerosolized antibiotic therapy is to eradicate P. aeruginosa in the airways after initial colonization. Early infection may be cleared for months to several years by several protocols, including oral ciprofloxacin and/or aerosolized colistin or tobramycin. However, once chronically established, P. aeruginosa infection is rarely eradicated.

**Intravenous Antibiotic Therapy**

For the patient who has progressive or unrelenting symptoms and signs despite intensive home measures, intravenous antibiotic therapy is indicated. This therapy is usually initiated in the hospital but may be

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**Table 403-7** Antimicrobial Agents for Cystic Fibrosis Lung Infection

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>ORGANISMS</th>
<th>AGENTS</th>
<th>DOSAGE (mg/kg/24 hr)</th>
<th>NO. DOSES/24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Staphylococcus aureus</td>
<td>Dicloxacillin</td>
<td>25-50</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linezolid</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cephalaxin</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clindamycin</td>
<td>10-30</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amoxicillin-clavulanate</td>
<td>25-45</td>
<td>2-3</td>
</tr>
<tr>
<td></td>
<td>Haemophilus influenzae</td>
<td>Amoxicillin</td>
<td>50-100</td>
<td>2-3</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas aeruginosa</td>
<td>Ciprofloxacin</td>
<td>20-30</td>
<td>2-3</td>
</tr>
<tr>
<td></td>
<td>Burkholderia cepacia</td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>8-10&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2-4</td>
</tr>
<tr>
<td>Empirical</td>
<td></td>
<td>Azithromycin</td>
<td>10, day 1; 5, days 2-5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin</td>
<td>30-50</td>
<td>3-4</td>
</tr>
<tr>
<td>Intravenous</td>
<td>S. aureus</td>
<td>Nafcillin</td>
<td>100-200</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin</td>
<td>40</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tobramycin</td>
<td>8-12</td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amikacin</td>
<td>15-30</td>
<td>2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ticarcillin</td>
<td>400</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Piperacillin</td>
<td>300-400</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ticarcillin-clavulanate</td>
<td>400</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Piperacillin-tazobactam</td>
<td>240-400</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meropenem</td>
<td>60-120</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem-cilastatin</td>
<td>45-100</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td>150</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>B. cepacia</td>
<td>Aztreonam</td>
<td>150-200</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chloramphenicol</td>
<td>50-100</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meropenem</td>
<td>60-120</td>
<td>3</td>
</tr>
<tr>
<td>Aerosol</td>
<td></td>
<td>Tobramycin (inhaled)</td>
<td>300&lt;sup&gt;§&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aztreonam (inhaled)</td>
<td>75</td>
<td>3</td>
</tr>
</tbody>
</table>

*Quantity of trimethoprim.
<sup>1</sup>Quantity of ticarcillin.
<sup>2</sup>Quantity of piperacillin.
<sup>3</sup>In mg per dose.
completed on an ambulatory basis. Although many patients show improvement within 7 days, it is usually advisable to extend the period of treatment to at least 14 days. Permanent intravenous access can be provided for long-term or frequent courses of therapy in the hospital or at home. Thrombophilia screening should be considered before the use of totally implantable intravenous devices or for recurring problems with venous catheters.

Table 403-7 lists commonly used intravenous antibiotics. In general, treatment of Pseudomonas infection requires 2-drug therapy. A third agent may be required for optimal coverage of S. aureus or other organisms. The aminoglycosides have a relatively short half-life in many patients with CF. The initial parenteral dose, noted in Table 403-7, is generally given every 8 hr. After blood levels have been determined, the total daily dose should be adjusted. Peak levels of 10-15 mg/L are desirable, and trough levels should be kept at <2 mg/L to minimize the risk of ototoxicity and nephrotoxicity. The regimen of once-daily tobramycin dosing has been demonstrated to have equivalent efficacy and the advantage of decreased toxicity over dosing every 8 hr. For once-daily dosing of tobramycin, peak levels should be between 20 and 30 mg/L and trough levels should be 1 mg/L or less. In children, older children, and adults, once-daily intravenous tobramycin therapy is becoming the standard of care. Changes in therapy should be guided by lack of improvement and by culture results. If patients do not show improvement, complications such as heart failure and reactive airways or infection with viruses, Aspergillus fumigatus (see Chapter 237), non-tuberculous mycobacteria (see Chapters 217 and 399), or other unusual organisms should be considered. B. cepacia complex is the most frequent of a growing list of Gram-negative rods that may be particularly refractory to antimicrobial therapy. Infection control in both the outpatient and inpatient medical setting is critically important to prevent nosocomial spread of resistant bacterial organisms between patients.

Bronchodilator Therapy
Reversible airway obstruction occurs in many children with CF, sometimes in conjunction with frank asthma or acute bronchopulmonary aspergillosis. Reversible obstruction is defined as improvement of ≥12% in flow rates after inhalation of a bronchodilator. In many patients with CF, flow rates may improve by only 5-10%, however. Nevertheless, subjective benefit is claimed by many following use of a β-adrenergic agonist aerosol. Cromolyn sodium and ipratropium hydrochlorides are alternative agents, but there is no evidence to support their use.

Antiinflammatory Agents
Corticosteroids are useful for the treatment of allergic bronchopulmonary aspergillosis and severe reactive airway disease occasionally encountered in children with CF. Prolonged treatment of standard CF lung disease using an alternate-day regimen initially appeared to improve pulmonary function and diminish hospitalization rates. However, a 4-yr double-blind, multicenter study of this regimen for patients with mild to moderate lung disease found only modest efficacy and prohibitive side effects, including growth retardation, cataracts, and abnormalities of glucose tolerance at a dose of 2 mg/kg and growth retardation at 1 mg/kg. Inhaled corticosteroids have theoretical appeal, but there are few data documenting their efficacy and safety; it appears that discontinuing inhaled corticosteroids in patients with CF had no effect on lung function, antibiotic use, or bronchodilator use. Ibufrofen, given long term (dose adjusted to achieve a peak serum concentration of 50-100 μg/mL) for 4 yr, is associated with a slowing of disease progression, particularly in younger patients with mild lung disease. Side effects of nonsteroidal antiinflammatory drugs have been encountered (see Table 403-6); therefore, this therapy has not gained broad acceptance even though ibuprofen is the only antiinflammatory agent with documented efficacy in the patient population.

Endoscopy and Lavage
Treatment of obstructed airways sometimes includes tracheobronchial suctioning or lavage, especially if atelectasis or mucoid impaction is present. Bronchopulmonary lavage can be performed by the instillation of saline or a mucolytic agent through a fiberoptic bronchoscope. Antibiotics (usually gentamicin or tobramycin) can also be instilled directly at lavage in order to transiently achieve a much higher endobronchial concentration than can be obtained by using intravenous therapy. There is no evidence for sustained benefit from repeated endoscopic or lavage procedures.

Other Therapies
Expectorants such as iodides and guaifenesin do not effectively assist with the removal of secretions from the respiratory tract. Inspiratory muscle training can enhance maximum oxygen consumption during exercise as well as FEV₁.

Emerging Therapies
A major breakthrough in CF therapy is ivacaftor, a small molecule potentiator of the CFTR mutation, G551D (present in ~5% of patients). Ivacaftor activates the CFTR-G551D mutant protein, a class III CFTR mutation that results in protein localized to the plasma membrane but loss of chloride channel function. Ivacaftor therapy resulted in improvement in FEV₁ by an average of 10.6%, decreased the frequency of pulmonary exacerbations by 55%, decreased sweat chloride by an average of 48 mEq/L, and increased weight gain by an average of 2.7 kg. Ivacaftor is approved for CFTR-G551D patients 26 yr old, as a 150 mg, twice per day, oral therapy. Additional small molecule correctors are being tested for use in combination with Ivacaftor to correct the processing of the most common CFTR mutation, F508del. The goal of this strategy is to correct the localization of the protein to the apical membrane of the cell and then to potentiate its function.

TREATMENT OF PULMONARY COMPLICATIONS
Atelectasis
Lobar atelectasis occurs relatively infrequently; it may be asymptomatic and noted only at the time of a routine chest radiograph. Aggressive intravenous therapy with antibiotics and increased chest PT directed at the affected lobe may be effective. If there is no improvement in 5-7 days, bronchoscopic examination of the airways may be indicated. If the atelectasis does not resolve, continued intensive home therapy is indicated, because atelectasis may resolve during a period of weeks or months. Lobectomy should be considered only if expansion is not achieved and the patient has progressive difficulty from fever, anorexia, and unrelenting cough (see Chapter 408).

Hemoptysis
Endobronchial bleeding usually reflects airway wall erosion secondary to infection. With increasing numbers of older patients, hemoptysis has become a relatively frequent complication. Blood streaking of sputum is particularly common. Small-volume hemoptysis (<20 mL) should not trigger panic and is usually viewed as a need for intensified antimicrobial therapy and chest PT. When the hemoptysis is persistent or increases in severity, hospital admission is indicated. Massive hemoptysis, defined as total blood loss of ≥250 mL in a 24-hr period, is rare in the 1st decade and occurs in <1% of adolescents, but it requires close monitoring and the capability to replace blood losses rapidly. Chest PT is often discontinued until 12-24 hr after the last brisk bleeding episode and is then gradually re-instituted. Patients should receive vitamin K for an abnormal prothrombin time. During brisk hemoptysis, the child and parents require a great deal of reassurance that the bleeding will stop. Blood transfusion is not indicated unless there is hypotension or the hematocrit is significantly reduced. Ticarcillin, salicylates, and nonsteroidal antiinflammatory drugs interfere with platelet function and may aggravate hemoptysis. Bronchoscopy rarely reveals the site of bleeding. Lobectomy is to be avoided, if possible, because functioning lung should be preserved. Bronchial artery embolization can be useful to control persistent, significant hemoptysis.

Pneumothorax
Pneumothorax (see Chapter 411) is encountered in <1% of children and teenagers with CF, although it is more frequently encountered in...
older patients and may be life-threatening. The episode may be asymptomatic but is often attended by chest and shoulder pain, shortness of breath, or hemoptysis. A small air collection that does not grow can be observed closely. Chest tube placement with or without pleurodesis is often the initial therapy. Intravenous antibiotics are also begun on admission. An open thoracotomy or video-assisted thoracoscopic with plication of blebs, apical pleural stripping, and basal pleural abrasion should be considered if the air leak persists. Surgical intervention is usually well tolerated even in cases of advanced lung disease. The thoracotomy tube is removed as soon as possible, usually on the 2nd or 3rd postoperative day. The patient can then be mobilized, and full postural drainage therapy resumed. Previous pneumothorax with or without pleurodesis is not a contraindication to subsequent lung transplantation.

**Allergic Bronchopulmonary Aspergillosis**

Allergic bronchopulmonary aspergillosis occurs in 5-10% of patients with CF and may manifest as wheezing, increased cough, shortness of breath, and marked hyperinflation (see Chapters 237 and 399). In some patients, a chest radiograph shows new, focal infiltrates. The presence of rust-colored sputum, the recovery of *Aspergillus* organisms from the sputum, a positive skin test for *A. fumigatus*, the demonstration of specific immunoglobulin (Ig) E and IgG antibodies against *A. fumigatus*, or the presence of eosinophils in a fresh sputum sample supports the diagnosis. The serum IgE level is usually high. Treatment is directed at controlling the inflammatory reaction with oral corticosteroids. For refractory cases, oral antifungals may be required.

**Nontuberculous Mycobacteria Infection**

See Chapter 217.

Injured airways with poor clearance may be colonized by *Mycobacterium avium-complex* but also *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium kansasii*. Distinguishing endobronchial colonization (frequent) from invasive infection (infrequent) is challenging. Persistent fevers and new infiltrates or cystic lesions coupled with the finding of acid-fast organisms on sputum smear suggest infection. Treatment is prolonged and requires multiple antimicrobial agents. Symptoms may improve, but the nontuberculous mycobacteria are not usually cleared from the lungs.

**Bone and Joint Complications**

Hypertrophic osteoarthropathy causes elevation of the periosteum over the distal portions of long bones and bone pain, overlying edema, and joint effusions. Acetaminophen or ibuprofen may provide relief. Control of lung infection usually reduces symptoms. Intermittent arthropathy unrelated to other rheumatologic disorders occurs occasionally, has no recognized pathogenesis, and usually responds to non-steroidal antiinflammatory agents. Back pain or rib fractures from vigorous coughing may require pain management to permit adequate airway clearance. These and other fractures may stem from diminished bone mineralization, the result of reduced vitamin D absorption, corticosteroid therapy, diminished weight-bearing exercises, and, perhaps, other factors. There may be a bone phenotype in CF that is unrelated to therapies or nutritional status and may be due to CFTR dysfunction.

**Sleep-Disordered Breathing**

Particularly with advanced pulmonary disease and during chest exacerbations, individuals with CF may experience more sleep arousals, less time in rapid eye movement sleep, nocturnal hypoxemia, hypercapnia, and associated neurobehavioral impairment. Nocturnal hypoxemia may hasten the onset of pulmonary hypertension and right-sided heart failure. Efficacy of specific interventions for this complication of CF has not been systematically assessed. Prompt treatment of airway symptoms and nocturnal oxygen supplementation or bilevel positive airway pressure support should be considered in selected cases.

**Acute Respiratory Failure**

Acute respiratory failure (see Chapter 71) rarely occurs in patients with mild to moderate lung disease and is usually the result of a severe viral or other infectious illness. Because patients with this complication can regain their previous status, intensive therapy is indicated. In addition to aerosol, postural drainage, and intravenous antibiotic treatment, oxygen is required to raise the arterial PaO₂. An increasing Pco₂ may require ventilatory assistance. Endotracheal or bronchoscopic suction may be necessary to clear airway inspissated secretions and can be repeated daily. Right-sided heart failure should be treated vigorously. Recovery is often slow. Intensive intravenous antibiotic therapy and postural drainage should be continued for 1-2 wk after the patient has regained baseline status.

**Chronic Respiratory Failure**

Patients with CF acquire chronic respiratory failure after prolonged deterioration of lung function. Although this complication can occur at any age, it is now seen most frequently in adult patients. Because a long-standing PaO₂ <50 mm Hg promotes the development of right-sided heart failure, patients usually benefit from low-flow oxygen to raise arterial Po₂ to 55 mm Hg. Increasing hypercapnia may prevent the use of optimal fraction of inspired oxygen. Most patients improve somewhat with intensive antibiotic and pulmonary therapy measures and can be discharged from the hospital. Low-flow oxygen therapy is needed at home, especially with sleep. Noninvasive ventilatory support can improve gas exchange and has been documented to enhance quality of life. Ventilatory support may be particularly useful for patients awaiting lung transplantation. These patients usually display cor pulmonale and should reduce their salt intake and be given diuretics. Caution should be exercised to avoid ventilation-suppressing metabolic alkalosis that results from CF-related chloride depletion and, in many cases, from diuretic-induced bicarbonate retention. Chronic pain (headache, chest pain, abdominal pain, and limb pain) is frequent at the end of life and responds to judicious use of analgesics, including opioids. Dyspnea has been ameliorated with nebulized fentanyl.

Lung transplantation is an option for end-stage lung disease (see Chapter 443) but a topic of vigorous debate. Criteria for referral continue to be a subject of investigation and ideally include estimates of longevity with and without transplant based on lung function and exercise tolerance data. Because of bronchiolitis obliterans (see Chapter 394.1) and other complications, transplanted lungs cannot be expected to function for the lifetime of a recipient, and repeat transplantation is increasingly common. The demand for donor lungs exceeds the supply, and waiting lists as well as duration of waits continue to grow. The protocol for matching donor organs with lung transplant recipients has been revised to account for the severity of the patients’ lung disease. In a review of lung transplantation in children with CF between 1992 and 2002, pretransplant colonization with *B. cepacia*, diabetes, and older age decreased posttransplant survival. The review suggests that transplantation is often associated with many complications and may not prolong life nor significantly improve its quality.

**Heart Failure**

Some patients experience reversible right-sided heart failure (see Chapter 442) as the result of an acute event such as a viral infection or pneumothorax. Individuals with long-standing, advanced pulmonary disease, especially those with severe hypoxemia (PaO₂ <50 mm Hg), often acquire chronic right-sided heart failure. The mechanisms include hypoxic pulmonary arterial constriction and loss of the pulmonary vascular bed. Pulmonary arterial wall changes contribute to increased vascular resistance with time. Evidence for concomitant left ventricular dysfunction is often found. Cyanosis, increased shortness of breath, increased liver size with a tender margin, ankle edema, jugular venous distention, an unusual weight gain, increased heart size seen on chest radiograph, or evidence for right-sided heart enlargement on electrocardiogram or echocardiogram helps to confirm the diagnosis. Diuresis induced by furosemide (1 mg/kg administered intravenously) confirms the suspicion of fluid retention. Repeated doses are often required at 24-48 hr intervals to reduce fluid accumulation and accompanying symptoms. Concomitant use of spironolactone may protect against potassium depletion and facilitate long-term diuresis. Hypocholemic alkalosis complicates the long-term use of
loop diuretics. Digitalis is not effective in pure right-sided failure but may be useful when there is an associated left-sided dysfunction. The arterial $P_o_2$ should be maintained at $>50$ mm Hg if possible. Intensive pulmonary therapy, including intravenous antibiotics, is most important. Initially, the salt intake should be limited. Volume overload and antibiotics with high sodium content should be avoided. No clear-cut long-term benefit from pulmonary vasodilators has been demonstrated. The prognosis for heart failure is poor, but a number of patients survive for $\geq 25$ yr after the appearance of heart failure. Heart-lung transplantation may be an option (see preceding section).

**Nutritional Therapy**

Up to 90% of patients with CF have loss of exocrine pancreatic function as well as inadequate digestion and absorption of fats and proteins. They require dietary adjustment, pancreatic enzyme replacement, and supplementary vitamins. In general, children with CF need to exceed the usual required daily caloric intake to grow. Daily supplements of the fat-soluble vitamins are required.

**Diet**

Historically, at the time of diagnosis many infants presented with nutritional deficits; this situation is changing because of newborn screening. Sometimes young infants with a history of wheezy breathing were often started on soy-protein formulas prior to their evaluation; they did not use this protein well and often acquired hypoproteinemia with anasarca. Although in the past a low-fat, high-protein, high-calorie diet was generally recommended for older children, it resulted in deficiencies of essential fatty acids and poor growth. With the advent of improved pancreatic enzyme products, increased amounts of fat in the diet are well tolerated and preferred.

Most individuals with CF have a higher-than-normal caloric need because of increased work of breathing and perhaps because of increased metabolic activity related to the basic defect. When anorexia of chronic infection supervenes, weight loss occurs. Encouragement to eat high-calorie foods is important, but weight gain is not generally realized unless lung infection is controlled. Weight stabilization or gain sometimes requires nocturnal feeding via nasogastric tube or percutaneously. However, the advent of enteral feedings has allowed for significant weight gain in children with CF. Enteric-coated pancreatic enzyme products that are available in capsule form are preferred because they are absorbed in the small intestine. The dose of enzymes required usually increases with age, but caloric needs and enzyme dosages must be individualized for each patient. Enteric-coated pancreatic enzyme granules reduce but do not fully correct stool fat and nitrogen losses. Enzyme deficiency is limited, and correction with pancreatic enzyme replacement is critical.

Pancreatic exocrine replacement therapy given with ingested food reduces but does not fully correct stool fat and nitrogen losses. Enzyme dosage and product should be individualized for each patient. Enteric-coated, pH-sensitive enzyme microspheres are most often prescribed. Several strengths up to 25,000 IU of lipase/capsule are available. Administration of excessive doses has been linked to *colonic strictures* requiring surgery. Consequently, enzyme replacement should not exceed 2,500 lipase units/kg/meal in most circumstances. In general, infants need 2,000–4,000 lipase units per feeding, which is most easily given mixed with applesauce on a spoon. Snacks should also be covered. The dose of enzymes required usually increases with age, but some patients have lower requirements as teenagers and young adults. Some individuals require proton pump inhibitor therapy to correct acid pH in the duodenum which is due to lack of exocrine pancreatic secretions; neutralization of duodenal pH permits activation of enteric-coated pancreatic exocrine replacement therapy granules.

**Vitamin and Mineral Supplements**

Because pancreatic insufficiency results in malabsorption of fat-soluble vitamins (A, D, E, K), vitamin supplementation is recommended. Several vitamin preparations containing all 4 vitamins for patients with CF are available. They should be taken daily. Replacement doses may be required when low serum levels are documented or the patient is symptomatic. Infants with zinc deficiency and an acrodermatitis enteropathica–like rash have been described. In addition, attention should be paid to iron status; in one study, almost 30% of children with CF had low serum ferritin concentrations.

**TREATMENT OF INTESTINAL COMPLICATIONS**

### Meconium Ileus

When meconium ileus (see Chapter 102.1) is suspected, a nasogastric tube is placed for suction and the newborn is hydrated. In many cases, diatrizoate (Gastrografin) enemas with reflux of contrast material into the ileum not only confirm the diagnosis but have also resulted in the passage of a meconium plug and clearing of the obstruction. Use of this hypertonic solution requires careful correction of water losses into the bowel. Children in whom this procedure fails require operative intervention. Children who are successfully treated generally have a prognosis similar to that of other patients with severe CF mutations. Infants with meconium ileus should be treated as if they have CF until adequate diagnostic testing can be carried out.

### Distal Intestinal Obstruction Syndrome (Meconium Ileus Equivalent) and Other Causes of Abdominal Symptoms

Despite appropriate pancreatic enzyme replacement, 2-5% of patients accumulate fecal material in the terminal portion of the ileum and in the cecum, which may result in partial or complete obstruction. For intermittent symptoms, pancreatic enzyme replacement should be continued or even increased, and stool softeners (polyethylene glycol [MiraLAX] or docusate sodium [Colace]) given. Increased fluid intake is also recommended. Failure to relieve symptoms signals the need for large-volume bowel lavage with a balanced salt solution containing polyethylene glycol taken by mouth or by nasogastric tube. When there is complete obstruction, a diatrizoate enema, accompanied by large amounts of intravenous fluids, can be therapeutic. Intussusception (see Chapter 333.3) and volvulus (see Chapter 329.4) must also be considered in the differential diagnosis. Intussusception, usually ileocolic, occurs at any age and often follows a 1–2 day history of “constipation.” It can often be diagnosed and reduced via a diatrizoate enema. If a nonreducible intussusception or a volvulus is present, laparotomy is required. Repeated episodes of intussusception may be an indication for cecectomy.

Chronic appendicitis with or without peripendipetal abscess may manifest as recurrent or persistent abdominal pain, raising the question of need for a laparotomy. A lack of acid buffering in the duodenum appears to promote duodenitis and ulcer formation in some children. Other reasons for surgical procedures include carcinoma of the colon or biliary tract and sclerosing colonopathy.

### Gastroesophageal Reflux

See Chapter 323.

Because several factors raise intraabdominal pressure, including cough and obstructed airways, pathologic gastroesophageal reflux is not uncommon and may exacerbate lung disease secondary to reflex wheezing and repeated aspiration. Dietary, positional, and medication therapies should be considered. Cholinergic agonists are contraindicated because they trigger mucus secretion and progressive respiratory difficulty. Reduction of stomach acid secretion can help, with proton pump inhibitors being the most effective agents. Fundoplication is a procedure of last resort.

### Rectal Prolapse

See Chapter 344.5.

Though uncommon, rectal prolapse occurs most often in infants with CF, and less frequently in older children with the disease. It is usually related to steatorrhea, malnutrition, and repetitive cough. The prolapsed rectum can usually be replaced manually by continuous gentle pressure with the patient in the knee-chest position. Sedation...
may be helpful. To prevent an immediate recurrence, the buttocks can be taped closed. Adequate pancreatic enzyme replacement, decreased fat and roughage in the diet, stool softener, and control of pulmonary infection result in improvement. Occasionally, a patient may continue to have rectal prolapse and may require sclerotherapy or surgery.

**Hepatobiliary Disease**

Liver function abnormalities associated with biliary cirrhosis can be improved by treatment with ursodeoxycholic acid. The ability of bile acids to prevent progression of cirrhosis has not been clearly documented. Portal hypertension with esophageal varices, hypersplenism, or ascites occurs in ≤8% of children with CF (see Chapter 367). The acute management of bleeding esophageal varices includes nasogastric suction and cold saline lavage. Sclerotherapy is recommended after an initial hemorrhage. In the past, significant bleeding has also been treated successfully with portosystemic shunting. Splenorenal anastomosis has been the most effective treatment. Pronounced hypersplenism may require splenectomy. Cholelithiasis should prompt surgical consultation. The management of ascites is discussed in Chapter 370.

Obstructive jaundice in newborns with CF needs no specific therapy. Hepatomegaly with steatosis requires careful attention to nutrition and may respond to carnitine repletion. Rarely, biliary cirrhosis proceeds to hepatocellular failure, which should be treated as in patients without CF (see Chapters 364 and 367). End-stage liver disease is an indication for liver transplantation in children with CF, especially if pulmonary function is good (see Chapter 368).

**Pancreatitis**

Pancreatitis can be precipitated by fatty meals, alcohol ingestion, or tetracycline therapy. Serum amylase and lipase values may remain elevated for long periods. Treatment of this disorder is discussed in Chapter 351.

**Hyperglycemia**

Onset of hyperglycemia occurs most frequently after the 1st decade. Approximately 20% of young adults are treated for hyperglycemia, although the incidence of CF-related diabetes may be up to 50% in CF adults. Prevalence is greater in females and in F508del homozygotes. Ketoacidosis is rarely encountered. The pathogenesis includes both impaired insulin secretion and insulin resistance. Routine screening consists of an annual modified 2-hr oral glucose tolerance test after the child reaches age 10 yr. Glucose intolerance without urine glucose losses is usually not treated; glycosylated hemoglobin levels should be followed at least annually. With persistent glucosuria and symptoms, insulin treatment should be instituted. Oral hypoglycemic agents, with or without drugs that reduce insulin resistance, may also be effective. Exocrine pancreatic insufficiency and malabsorption make strict dietary control of hyperglycemia difficult. Corticosteroid therapy should be avoided. The development of significant hyperglycemia favors acquisition of *P. aeruginosa* and *B. cepacia* in the airways and may adversely affect pulmonary function. Thus, careful control of blood glucose level is an important goal. Long-term vascular complications of diabetes can occur, providing an additional rationale for good control of blood glucose levels.

**OTHER THERAPY**

**Nasal Polyps**

Nasal polyps (see Chapter 378) occur in 15-20% of patients with CF and are most prevalent in the 2nd decade of life. Local corticosteroids and nasal decongestants occasionally provide some relief. When the polyps completely obstruct the nasal airway, rhinorrhea becomes constant, or widening of the nasal bridge is noticed, surgical removal of the polyps is indicated; polyps may recur promptly or after a symptom-free interval of months to years. Polyps inexplicably stop developing in many adults.

**Rhinosinusitis**

Opacification of paranasal sinuses is not an indication for intervention. Acute or chronic sinus-related symptoms are treated initially with antimicrobials, with or without maxillary sinus aspiration for culture. Functional endoscopic sinus surgery has anecdotaly provided benefit.

**Salt Depletion**

Salt losses from sweat in patients with CF can be high, especially in warm arid climates. Children should have free access to salt, and precautions against overdressing infants should be observed. Salt supplements are often prescribed to newborns identified through newborn screening and to children who live in hot weather climates. Hypochloremic alkalosis should be suspected in any infant who has had symptoms of gastroenteritis, and prompt fluid and electrolyte therapy should be instituted as needed.

**Growth and Maturation**

Delayed growth should be vigorously addressed by enhancing nutrition, treating lung disease more vigorously, and, in selected instances, endocrine evaluation and, possibly, growth hormone therapy. The risk:benefit ratio for anabolic steroid therapy does not support its use for undersized children with CF. Delayed sexual maturation, often associated with short stature, occurs fairly frequently in children with CF. Although many patients have severe pulmonary infection or poor nutrition, delayed puberty also occurs in those with otherwise mild disease and is not well explained. Adolescents with CF should receive specific counseling throughout their developing years concerning sexual maturation and reproductive potential.

**Surgery**

Minor surgical procedures, including dental work, should be performed with the use of local anesthesia if possible in children with CF. Patients with good or excellent pulmonary status can tolerate general anesthesia without any intensive pulmonary measures before the procedure. Those with moderate or severe pulmonary infection usually do better with a 1-2 wk course of intensive antibiotic treatment and increased airway clearance before surgery. If this approach is impossible, prompt intravenous antibiotic therapy is indicated once it is recognized that major surgery is required. The total time of anesthesia should be kept to a minimum. After induction, tracheal suctioning is useful and should be repeated. Patients with severe disease require monitoring of blood gas values and may need ventilatory assistance in the immediate postoperative period.

After major surgery, cough should be encouraged and airway clearance treatments should be re-instituted as soon as possible, usually within 24 hr. Adequate analgesia is important if early effective therapy is to be achieved. For those with significant pulmonary involvement, intravenous antibiotics are continued for 7-14 days postoperatively. Early ambulation and intermittent deep breathing are important; an incentive spirometer can also be helpful. After open thoracotomy for treatment of pneumothorax or lobectomy, the chest tube is the greatest single obstacle to effective pulmonary therapy and should be removed as soon as possible so that full postural drainage therapy can resume.

**PROGNOSIS**

CF remains a life-limiting disorder, although survival has improved dramatically in the past 30-40 yr. Infants with severe lung disease occasionally succumb, but most children survive this difficult period and are relatively healthy into adolescence or adulthood. The slow progression of lung disease eventually reaches disabling proportions. Life table data now indicate a median cumulative survival of 37 yr. Male survival is somewhat better than female survival for reasons that are not readily apparent. Children in socioeconomically disadvantaged families have, on average, a poorer prognosis.

Children with CF usually have good school attendance records and should not be restricted in their activities. A high percentage eventually attend and graduate from college. Most adults with CF find satisfactory employment, and an increasing number marry. Transitioning care from pediatric to adult care centers by 21 yr of age is an important objective and requires a thoughtful, supportive approach involving both the pediatric and internal medicine specialists.
With increasing life span for patients with CF, a new set of psychosocial considerations has emerged, including dependence-independence issues, self-care, peer relationships, sexuality, reproduction, substance abuse, educational and vocational planning, medical care costs and other financial burdens, and anxiety concerning health and prognosis. Many of these issues are best addressed in an anticipatory fashion, before the onset of psychosocial dysfunction. With appropriate medical and psychosocial support, children and adolescents with CF generally cope well. Achievement of an independent and productive adulthood is a realistic goal for many.

Bibliography is available at Expert Consult.


Primary ciliary dyskinesia (PCD) is an inherited disorder characterized by impaired ciliary function leading to diverse clinical manifestations, including chronic sinopulmonary disease, persistent middle ear effusions, laterality defects, and infertility. Although the estimated frequency of PCD is 1 in 12,000 to 1 in 20,000 live births, its prevalence in children with repeated respiratory infections has been estimated to be as high as 5%.

NORMAL CILIARY ULTRASTRUCTURE AND FUNCTION
Three types of cilia exist in the humans: motile cilia; primary (sensory) cilia; and nodal cilia.

**Motile cilia** are hair-like organelles that move fluids, mucous, and inhaled particulates vectorially from conducting airways, paranasal sinuses, and eustachian tubes. The upper and lower respiratory tracts are continuously exposed to inhaled pathogens, and local defenses have evolved to protect the airway. The respiratory epithelium in the nasopharynx, middle ear, paranasal sinuses, and larger airways are lined by a ciliated, pseudostratified columnar epithelium that is essential for mucociliary clearance (Fig. 404-1). A mature ciliated epithelial cell has approximately 200 uniform motile cilia that are anatomically and functionally oriented in the same direction, moving with intracellular and intercellular synchrony. Anchored by a basal body to the apical cytoplasm and extending from the apical cell surface into the airway lumen, each cilium is a complex, specialized structure, composed of hundreds of proteins. It contains a cylinder of microtubule doublets organized around a central pair of microtubules (Fig. 404-2), leading to the characteristic “9+2” arrangement seen on cross-sectional views on transmission electron microscopy. A membrane continuous...
with the plasma membrane covers the central fibrillar structure, or axoneme. The ciliary axoneme is highly conserved across species, and the structural elements of simple protozoan flagella and the mammalian cilium are similar. Attached to the A microtubules as distinct inner and outer dynein arms, multiple different adenosine triphosphatases, called dyneins, serve as “motors” of the cilium and promote microtubule sliding, which is converted into bending. The inner dynein arm influences the bend shape of the cilium, whereas the outer dynein arm controls beat force and frequency. Nexin links connect adjacent outer microtubular doublets limit the degree of sliding between microtubules, and with the radial spokes are controlled by the dynein regulatory complex. The result is a ciliary stroke and coordinated beating at a frequency constant throughout the airway, 8-20 beats/sec, but can be negatively affected by several factors, such as anesthetics and dehydration. Alternatively, beat frequency may be accelerated by exposure to irritants or bioactive molecules, including β-adrenergic agents, acetylcholine, and serotonin. Cilia beat frequency can be increased through the activity of nitric oxide synthases that are localized in the apical cytoplasm. The coordinated wave-like pattern of ciliary motion has important functions in fluid and cell movement, and any disturbance in the precise, orchestrated movement of the cilia can lead to disease.

Primary (sensory) cilia are present during interphase on most cell types. These cilia lack a central microtubule doublet and dynein arms, thus creating a “9+0” arrangement and leaving them immotile (see Fig. 404-2). For years, these structures were considered nonfunctional vestigial remnants, but primary cilia are important signaling organelles that sense the extracellular environment. They are mechanoreceptors, chemosensors, osmosensors, and, in specialized cases, defect changes in light, temperature, and gravity. Primary cilia are found on the surface of nondividing cells, including the renal nephron, bile ductules, chondrocytes, astrocytes, and cells in sensory organs. Defects are linked to wide-ranging pediatric conditions, such as various polycystic kidney diseases, nephronophthisis, Bardet-Biedl syndrome, Meckel-Gruber syndrome, Joubert syndrome, Alström syndrome, Ellis-van Creveld syndrome, and Jeune thoracic dystrophy.

The third distinct classification of cilia exists only during a brief period of embryonic development. These nodal cilia have a “9+0” microtubule arrangement similar to that of primary cilia, but they exhibit a whirling, rotational movement (see Fig. 404-2), resulting in leftward flow of extracellular fluid that establishes body sidedness. Nodal cilia defects result in body orientation abnormalities, such as situs inversus totalis, situs ambiguous, and heterotaxy associated with congenital heart disease, asplenia, and polysplenia (see Chapter 431.11).

GENETICS OF PRIMARY CILIARY DYSKINESIA

PCD is typically has autosomal recessive patterns of inheritance, although rare cases of autosomal dominant and X-linked inheritance have been reported. PCD is a genetically heterogeneous disorder involving multiple genes; mutations in any protein that is involved in ciliary assembly, structure, or function could theoretically cause disease. Early linkage analyses showed substantial locus heterogeneity, which made correlations between ciliary defects and the underlying mutations difficult. Numerous PCD-associated genes have been discovered. The advent of high-throughput sequencing technologies has allowed for even more rapid identification of new mutations in PCD subjects. To date, mutations in 18 different genes have been linked to PCD (Fig. 404-3), including those that encode proteins integral to the outer dynein arm (DNAH5, DNA11, DNA12, TXNDC3, and DNAH11), inner dynein arm and axonemal organization (CCDC39 and CCDC40), and the central apparatus and radial spokes (RSPH4A, RSPH4B, HYDIN). More recently, mutations in genes that code for cytoplasmic proteins involved in cilia assembly or protein transport (HEATR2, DNA1A1, DNA1A2, DNA1A3, CCDC103, LRRCC6, and CCDC114) have been shown to cause ultrastructural abnormalities. The genetics of PCD has further exposed the gaps in current diagnostic approaches. For instance, DNAH11 mutations have been shown to cause typical clinical phenotypes without apparent axonemal ultrastructural defects or reduced ciliary beat frequency. Mutations in other genes, CCDC39 and CCDC40, produce inconsistent structural abnormalities characterized by disordered microtubules in some, but not all, cilia, which underscores the observation that current diagnostic testing will miss cases.

CLINICAL MANIFESTATIONS OF PRIMARY CILIARY DYSKINESIA

See Table 404-1.

Most patients with PCD present with neonatal respiratory distress, which is manifested as tachypnea, hypoxemia, or even respiratory failure requiring mechanical ventilation. The association of respiratory distress in term neonates with PCD has been underappreciated. The upper respiratory tract is almost universally involved in PCD, and persistent rhinosinusitis is common during infancy. Inadequate innate mucus clearance leads to chronic sinusitis (see Chapter 380) and nasal polyposis. Middle ear disease occurs in nearly all children with PCD, with varying degrees of chronic otitis media leading to conductive hearing loss and myringotomy tube placement, which is often complicated by intractable otitis.

Impaired mucociliary clearance of the lower respiratory tract leads to daily productive cough, often in young children, secondary to chronic bronchiitis. Bacterial cultures of sputum or lavage fluid frequently yield nontypeable Haemophilus influenzae (see Chapter 194), Staphylococcus aureus (see Chapter 181.1), Strepococcus pneumoniae (see Chapter 182), and Pseudomonas aeruginosa (see Chapter 205.1). Persistent airway infection and inflammation lead to bronchiectasis,
even in preschool children. Clubbing is a sign of long-standing pulmonary involvement.

Left-right laterality defects (e.g., situs inversus totalis) are found in half of all children with PCD. Without functional nodal cilia in the embryonic period, thoracoabdominal orientation is random. These patients have Kartagener triad, defined as situs inversus totalis, chronic sinusitis, and bronchiectasis. Approximately 25% of patients with situs inversus totalis have PCD, so situs inversus totalis alone does not establish the diagnosis of PCD. Other laterality defects, such as heterotaxy, are associated with PCD and may coexist with congenital cardiac defects, asplenia, or polysplenia.

Most men with PCD have dysmotile spermatozoa because flagellar and ciliary ultrastructure is similar. Male infertility is typical, but not always found in this disease. Fertility issues in women have also been reported and are likely a result of ciliary dysfunction in the fallopian tubes.

A few case reports have associated neonatal hydrocephalus with PCD. The ependyma of the brain ventricles are lined by ciliated epithelium and are important for cerebrospinal fluid flow through the ventricles and aqueduct of Sylvius. The finding of enlarged brain ventricles on sonograms, when linked with situs inversus totalis, has been proposed as a prenatal diagnostic marker for PCD. X-linked retinitis pigmentosa has been associated with recurrent respiratory infections in families with RPGR gene mutations. Intraflagellar transport proteins are essential for photoreceptor assembly, and when mutated, lead to apoptosis of the retinal pigment epithelium (see Chapter 630).

### Diagnosis of Primary Ciliary Dyskinesia

The diagnosis of PCD should be suspected in children with chronic or recurring upper and lower respiratory tract symptoms that begin in early infancy and is currently based on the presence of characteristic clinical phenotype and ultrastructural defects of cilia, though this approach will miss affected individuals. The diagnosis is often delayed, even in children who have classic clinical features, such as chronic rhinosinusitis in infancy, persistent otitis media, or even situs inversus totalis. The average age at PCD diagnosis is approximately 4 yr; a high index of suspicion is necessary.

Imaging studies show extensive involvement of the paranasal sinuses. Chest radiographs frequently demonstrate bilateral lung over-inflation, peribronchial infiltrates, and lobar atelectasis. Computerized x-ray tomography of the chest often reveals bronchiectasis, often involving the anatomic right middle lobe or lingual, even in young children. Situs inversus totalis in a child who has chronic respiratory tract symptoms is highly suggestive of PCD, but this configuration occurs in only half of patients with PCD. Pulmonary function testing typically shows progressive intrathoracic airway obstruction.

Transmission electron microscopy is the current gold standard to assess structural defects within the cilium. Curetage from the nasal epithelium or endobronchial brushing can provide an adequate specimen for review. Identification of a discrete, consistent defect in any aspect of the ciliary structure with concurrent phenotypic features is sufficient to make the diagnosis. Shortening or absence of dynein arms is the most common abnormality seen in PCD, accounting for 90% of cases with defined ultrastructural defects (see Fig. 404-3). Other axonemal changes consistent with PCD include microtubular transposition, radial spoke and nexin link defects, and ciliary agenesis. Unfortunately, ultrastructural examination of cilia as a diagnostic test for PCD has significant drawbacks. First, the absence of axonemal defects does not exclude PCD; nearly 30% of all affected individuals have normal ciliary ultrastructure. Careful interpretation of the ultrastructural findings is necessary, because nonspecific changes may be seen in relation to exposure to environmental pollutants or infection. Ciliary defects can be acquired (Table 404-2). Acute airway infection or inflammation can result in structural changes (e.g., compound cilia or blebs). Ciliary disorientation has been proposed as a form of PCD, but this phenomenon is the result of airway injury. Frequently, the diagnosis of PCD can be delayed or missed because of inadequate tissue collection or sample processing as well as the lack of an experienced pathologist who can distinguish between primary and acquired ciliary defects. Several reviews have advocated culturing of airway epithelial cells and allowing the secondary changes to resolve.

### TREATMENT

No therapies correct ciliary dysfunction in PCD. Many of the treatments applied to PCD patients are similar to those used in other purpurative lung diseases characterized by impaired airway clearance and bronchiectasis, such as cystic fibrosis, but none have been adequately studied to demonstrate their efficacy in PCD.

Strategies to enhance mucociliary clearance are central to PCD therapy, and routine airway clearance techniques using postural

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**Table 404-2: Electron Microscopic Findings in Primary Ciliary Dyskinesia vs Acquired Cilia Abnormality**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>PCD</th>
<th>ACQUIRED DEFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal wave form</td>
<td>May be normal or abnormal</td>
<td>May be normal or abnormal</td>
</tr>
<tr>
<td>May be normal or reduced</td>
<td></td>
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</tr>
</tbody>
</table>

**EM ultrastructure**

- Dynein arm deficiency
  - Outer arms
  - Inner arms
- Compound cilia
- Added peripheral tubules
- Deleted peripheral tubules
- Added central pairs
- Translocation of central tubules
- Few or absent cilia (generalized)
- Few or absent cilia (patchy)

**Beat frequency**

- Hyperkinetic, slow or absent
- May be normal or reduced

drainage, percussion vests, positive expiratory pressure devices, or other techniques should be instituted on a daily basis. Because ciliary function is impaired, cough becomes a critical mechanism for mucus clearance and should not be suppressed. Exercise can enhance airway clearance in patients with PCD and should be encouraged. Inhaled mucolytic agents are often used in cystic fibrosis care, and few case reports have shown improvement in lung function in patients with PCD after treatment.

When children with PCD develop increasing respiratory symptoms consistent with infection, antimicrobial therapy should be instituted on the basis of respiratory culture results and bacterial sensitivities. Early eradication strategies to clear bacteria from the PCD lung have not been studied. Maintenance therapy with inhaled or oral antibiotics can be used cautiously in patients with PCD who have bronchiectasis or frequent exacerbations, although current literature lacks evidence supporting long-term antimicrobial therapy. Immunizations against pertussis, influenza, and pneumococci are cornerstones of care. Additional preventive measures include avoidance of cigarette smoke and other airway irritants.

Although β-adrenergic agonists increase ciliary beat frequency in normal epithelial cells, data is lacking that shows these agents improve function of dyskinetic cilia. Moreover, they do not necessarily provide bronchodilation in patients with PCD and obstructive airway disease.

Surgical resection of bronchiectatic lung has been performed on patients with PCD, typically in cases of localized disease with severe hemoptysis or recurrent febrile illnesses. It is unclear whether surgical interventions provide reduction in symptoms or survival benefit.

Progression to end-stage lung disease and respiratory failure has been reported in patients with PCD. Adult patients have undergone successful heart-lung, double lung, or living donor lobar lung transplantation. Situs inversus totalis complicates the procedure owing to anatomic considerations. Otherwise, survival is similar to that for other transplant recipients.

Treatment of chronic otitis media and middle ear effusions in patients with PCD is controversial. Myringotomy tubes are frequently placed in affected children, but they are not without complications, because they may lead to chronic mucoid otorrhea, tympanosclerosis, and permanent membrane perforation. Myringotomy tubes have not measurably improved hearing acuity. Although hearing tends to improve with time, it should be routinely screened and hearing aids used when necessary.

Chronic rhinitis and sinusitis are frequent clinical manifestations of PCD. No treatments have been shown to be effective, although patients are often treated with nasal washes, paranasal sinus lavage, and systemic antibiotics when they are symptomatic. As with any overuse of antimicrobial agents, the development of resistant organisms is a concern. When nasal symptoms are severe or refractory to medical management, endoscopic sinus surgery can be used to promote drainage or local delivery of medications, though the benefit may be short-lived.

**PROGNOSIS**

Although signs and symptoms related to upper respiratory involvement predominate early in PCD, clinical manifestations of lower respiratory tract disease tend to increase with age and become the leading cause of morbidity and mortality in PCD patients. It is believed that progression and extent of lung disease can be slowed with early diagnosis and therapy. Thus, routine surveillance studies recommended for the care of children with PCD include (1) regular spirometry to monitor pulmonary function, (2) chest imaging, and (3) sputum or oropharyngeal cultures to assess lung respiratory flora.

Patients with PCD typically have slower decline in pulmonary function than those with cystic fibrosis. Its prognosis and long-term survival are better. Many patients with PCD have a normal or near-normal life span, although some do experience progressive bronchiectasis and respiratory deterioration earlier in life.

*Bibliography is available at Expert Consult.*
Bibliography


Chapter 405
Diffuse Lung Diseases in Childhood

See also Chapter 399.

405.1 Inherited Disorders of Surfactant Metabolism
Lawrence M. Nogee, F. Sessions Cole III, and Aaron Hamvas

Pulmonary surfactant is a mixture of phospholipids and proteins synthesized, packaged, and secreted by alveolar type II pneumocytes (AEC2s) that line the distal air spaces. This mixture forms a monolayer at the air–liquid interface that lowers surface tension at end-expiration of the respiratory cycle, preventing atelectasis and ventilation–perfusion mismatch. Four surfactant-associated proteins have been described: surfactant proteins A and D (SP-A, SP-D) participate in host defense in the lung, whereas surfactant proteins B and C (SP-B, SP-C) contribute to the surface tension–lowering activity of the pulmonary surfactant. The adenosine triphosphate–binding cassette protein member A3, ABCA3, is a transporter located on the limiting membrane of lamellar bodies, the storage organelle for surfactant within alveolar type II cells, and has an essential role in surfactant phospholipid metabolism. The proper expression of the surfactant proteins and ABCA3 is dependent on a number of transcription factors, particularly thyroid transcription factor 1 (TTF-1). Two genes for SP-A (SFTPA1, SFTPA2) and 1 gene for SP-D (SFTPD) are located on human chromosome 10, whereas single genes encode SP-B (SFTPB), SP-C (SFTPC), TTF-1 (NKX2-1) and ABCA3 (ABCA3), which are located on human chromosomes 2, 8, 14, and 16, respectively. Inherited disorders of SP-B, SP-C, ABCA3 and TTF-1 have been identified in humans and are collectively termed surfactant dysfunction disorders (Table 405-1).

PATHOLOGY
Histopathologically, these disorders share a unique constellation of features, including AEC2 hyperplasia, alveolar macrophage accumulation, interstitial thickening and inflammation, and alveolar proteinosis. A number of different descriptive terms have historically been applied to these disorders, including ones borrowed from adult forms of interstitial lung disease (desquamative interstitial pneumonia, nonspecific interstitial pneumonia) as well as a disorder unique to infancy (chronic pneumonitis of infancy). These diagnoses in infants and children are strongly indicative of surfactant dysfunction disorders but do not distinguish which gene is responsible. As the prognosis and inheritance patterns differ depending upon the gene involved, genetic testing should be offered when one of these conditions is reported in the lung biopsy or autopsy of a child.

Deficiency of Surfactant Protein B (Surfactant Metabolism Dysfunction, Pulmonary, 1; SMDP1; OMIM #265120)
Clinical Manifestations
Infants with an inherited deficiency of SP-B present in the immediate neonatal period with respiratory failure. This autosomal recessive disorder is clinically and radiographically similar to the respiratory distress syndrome (RDS) of premature infants (see Chapter 101.3) but typically affects full-term infants. The initial degree of respiratory distress is variable, but the disease is progressive and is refractory to mechanical ventilation, surfactant replacement therapy, glucocorticoid
administered, and extracorporeal membrane oxygenation. SP-B deficiency is recognized in diverse racial and ethnic groups. Almost all affected patients have died without lung transplantation, but prolonged survival is possible in cases of partial deficiency of SP-B. Although murine lineages heterozygous for SP-B deficiency are susceptible to oxidant injury and pulmonary infection, humans heterozygous for loss-of-function mutations in SFTPB are clinically normal as adults but may be at increased risk for obstructive lung disease if they also have a history of smoking.

**Genetics**

Multiple loss-of-function mutations in SFTPB have been identified. The most common is a net 2 base-pair insertion in codon 121 (originally termed 121ins2) that results in a frameshift, an unstable SP-B transcript, and absence of SP-B protein production. This mutation has accounted for 60-70% of the alleles found to date in patients identified with SP-B deficiency. Most other mutations have been family specific. A large deletion encompassing 2 exons of the SP-B gene has also been reported.

**Diagnosis**

A rapid, definitive diagnosis can be established with sequence analysis of SFTPB, which is available through clinical laboratories (http://www.genetests.org). In families in which a mutation was previously identified, antenatal diagnosis can be established by molecular assays of DNA from chorionic villous biopsy or amniocytes, which permits advanced planning of a therapeutic regimen. Other laboratory tests remain investigational, including analysis of tracheal effluent by for the presence or absence of SP-B protein and for incompletely processed precursor proSP-C peptides that have been found in SP-B-deficient human infants and animals. Immunostaining of lung biopsy tissue for the surfactant proteins can also support the diagnosis, although immunohistochemical assays for SP-B and SP-C are also generally available only on a research basis. Staining for SP-B is usually absent, but robust extracellular staining for proSP-C because of incompletely processed proSP-C peptides is observed and is diagnostic for SP-B deficiency. Such studies require a lung biopsy in a critically ill child but may be performed on lung blocks acquired at the time of autopsy, allowing for retrospective diagnosis. With electron microscopy, a lack of tubular myelin, disorganized lamellar bodies, and an accumulation of abnormal-appearing multivesicular bodies, suggest abnormal lipid packaging and secretion.

**Surfactant Protein C Gene Abnormalities (Surfactant Metabolism Dysfunction, Pulmonary, 2; SMDP2; OMIM #610913)**

SP-C is a very low-molecular-weight, extremely hydrophobic protein that, along with SP-B, enhances the surface tension–lowering properties of surfactant phospholipids. It is derived from proteolytic processing of a larger precursor protein (proSP-C).

**Clinical Manifestations**

The clinical presentation of patients with SFTPC mutations is quite variable. Some patients present at birth with symptoms, signs, and radiographic findings typical of RDS. Others present later in life, ranging from early infancy until well into adulthood, with gradual onset of respiratory insufficiency, hypoxemia, failure to thrive, and chest radiograph demonstration of interstitial lung disease, or, in the 5th or 6th decade of life, as pulmonary fibrosis. The age and severity of disease vary even within families with the same mutation. The natural history is also quite variable, with some patients improving either spontaneously or as the result of therapy, some with persistent respiratory insufficiency, and some progressing to the point of requiring lung transplantation. This variability in severity and course of the disease does not appear to correlate with the specific mutation and also hinders accurate assessment of prognosis.

**Genetics**

Multiple mutations in SFTPC have been identified in association with acute and chronic lung disease in patients ranging in age from newborn to adult. A mutation on only 1 SFTPC allele is sufficient to cause disease. Approximately half of these mutations arise spontaneously, resulting in sporadic disease, but the remainder are inherited as a dominant trait. A threonine substitution for isoleucine in codon 73 (termed p.173T or p.Ile73Thr) accounts for 25-35% of the cases identified to date. Mutations in SFTPC are thought to result in production of misfolded proSP-C that accumulates within the alveolar type II cell and causes cellular injury, or alters the normal intracellular routing of proSP-C. The frequency of mutations or disease caused by mutations in SFTPC is unknown but is probably low. Mutations have been identified in diverse racial and ethnic groups.

**Diagnosis**

Sequencing of SFTPC, the only definitive diagnostic test, is available in clinical laboratories. The relatively small size of the gene facilitates such
analyses, which are quite sensitive, but because most SFTP-C mutations are missense mutations, distinguishing true disease-causing mutations from rare yet benign sequence variants may be difficult. Immunostaining of lung tissue may demonstrate proSP-C aggregates but is available only on a research basis.

**Disease Caused by Mutations in ABCA3 (Surfactant Metabolism Dysfunction, Pulmonary, 3; SMDF3; OMIM #610921)**

**Clinical Manifestations**
Lung disease caused by mutations in ABCA3 generally presents as either a severe, lethal form that manifests in the immediate newborn period clinically similar to SP-B deficiency, or a chronic form that appears most typically in the 1st yr of life with interstitial lung disease similar to SP-C-associated disease. Infants who are homozygous or compound heterozygous for null mutations, that is, the mutation is predicted to result in absence of protein expression, typically present with lethal neonatal disease, whereas infants with other types of mutations have more variable age of onset and outcomes. Heterozygosity for an ABCA3 mutation may contribute to the severity of RDS in prematurely born infants, who, in contrast to ABCA3-deficient infants with mutations on both alleles, may eventually completely recover from their initial lung disease.

**Genetics**
Recessive mutations in ABCA3 were first described in infants who presented with lethal respiratory distress in the newborn period, but now have been identified in older infants and children with interstitial lung disease. There is considerable allelic heterogeneity: More than 200 mutations scattered throughout the gene have been identified, most of which are family specific. A missense mutation that results in a valine substitution for glutamate in codon 292 (p.E292V or p.Glu292Val) in association with a second ABCA3 mutation has been found in children with severe neonatal respiratory failure and in older children with interstitial lung disease and is present in approximately 0.4% of the general population. ABCA3 mutations have been identified in diverse racial and ethnic groups. The precise frequency of disease is unknown, but large-scale sequencing projects indicate that the overall carrier rate for ABCA3 mutations may be as high as 1 in 50 to 1 in 70 individuals. ABCA3 deficiency may thus contribute to a substantial proportion of unexplained fatal lung disease in term infants and of interstitial lung disease in older children.

**Diagnosis**
Sequence analysis of ABCA3 is available in clinical laboratories and is the most definitive approach for diagnosis. Considerable variation in ABCA3 necessitates careful interpretation regarding the functionality of an individual variant and its contribution to the clinical presentation. Additionally, sequence analysis is not 100% sensitive as functionally significant mutations may exist in untranslated regions that are not generally analyzed. In these situations, lung biopsy with electron microscopy to examine lamellar body morphology may be a useful adjunct to the diagnostic approach. Small lamellar bodies that contain electron-dense inclusions may be observed in association with ABCA3 mutations. These findings support the hypothesis that ABCA3 function is necessary for lamellar body biogenesis. There are no biochemical markers to establish the diagnosis.

**Disease Caused by Mutations in NKX2-1 (Thyroid Transcription Factor 1, Choreaethetosis, Hypothyroidism, and Neonatal Respiratory Distress, OMIM #600635)**

**Clinical Manifestations**
A large deletion of the region of chromosome 14 (14q13.3) encompassing the NKX2-1 locus was first recognized in an infant with hypothyroidism and neonatal RDS. Since then, multiple large deletions involving the NKX2-1 locus and contiguous genes as well as missense, frameshift, nonsense, and small insertion or deletion mutations scattered throughout the gene have been reported in individuals with hypothyroidism, lung disease, and neurologic symptoms, including benign familial chorea. Manifestation of dysfunction in all 3 organ systems has been referred to as brain-thyroid-lung syndrome, but disease may manifest in only 1 or 2 organ systems. The lung disease can range from severe and eventually lethal neonatal respiratory distress to chronic lung disease in childhood and adulthood. Recurrent pulmonary infections have been reported, likely caused by reduced expression of the pulmonary collectins, SP-A and SP-D, but could also result from decreased expression of other proteins. No clear genotype-phenotype correlations have emerged, but children harboring complete gene deletions have tended to have more severe and earlier-onset disease. This observation could also be related to the deletion of other adjacent genes. While limited data are available, the pulmonary phenotype may depend upon the expression of which NKX2-1 target genes are most affected. Children with decreased SP-B or ABCA3 expression may present with acute neonatal respiratory failure whereas those with decreased SP-C or pulmonary collection expression are more likely to have chronic lung disease.

**Genetics**
The gene is small, spanning <3,000 bases, with only 3 exons. TTF-1 is expressed not only in the lung but also in the thyroid gland, as well as in the central nervous system. In the lung it is important for the expression of a wide variety of proteins, including the surfactant proteins, ABCA3, Clara cell secretory protein, and many others. Two transcripts that differ depending upon whether the transcriptional start site is in the 1st or 2nd exon have been recognized, although the shorter transcript is the predominant one in the lung. Most mutations are thought to result in a loss of function, with the mechanism of disease thus being haploinsufficiency, but discordant effects on different target genes have been reported. The incidence of mutations and incidence and prevalence of disease are unknown; mutations in diverse ethnic groups have been recognized. Most reported mutations and deletions have occurred de novo resulting in sporadic disease, but familial disease transmitted in a dominant manner has been recognized.

**Diagnosis**
Sequence analysis of the NKX2-1 gene is available through clinical laboratories and is the preferred method for diagnosis. As deletions comprise a significant fraction of reported mutant alleles, specific methods to look for such deletions should also be performed, such as a comparative genomic hybridization assay or multiplex ligation-dependent probe amplification assay. A mutation on 1 allele is sufficient to cause disease. While isolated pulmonary disease has been recognized, the majority of reported affected individuals have had manifestations in 1 or more other organ systems. Thus the presence of hypothyroidism or neurologic abnormality in a proband or a family history of chorea should prompt consideration of the diagnosis. The most specific neurologic finding is chorea, but hypotonia, developmental delay, ataxia, and dysarthria have been reported. In very young, nonambulatory infants the neurologic symptoms may not be evident, or muscle weakness or hypotonia may be attributed to the severity of lung disease or a result of the hypothyroidism. Affected individuals may not be overtly hypothyroid but have compensated hypothyroidism with borderline low T4 (thyroxine) and high thyroid-stimulating hormone levels. The lung pathology associated with NKX2-1 mutations may be typical of that of other surfactant dysfunction disorders, but because NKX2-1 is important for lung development, growth abnormalities and arrested pulmonary development also may be seen. Immunostaining studies of surfactant protein expression have yielded variable results, with decreased expression of 1 or more surfactant-related proteins observed in some patients. No characteristic electron microscopy findings have been identified.

**TREATMENT OF SURFACTANT Dysfunction Disorders**

Virtually all patients with SP-B deficiency die within the 1st yr of life. Conventional neonatal intensive care interventions can maintain extrapulmonary organ function for a limited time (weeks to months).
Replacement therapy with commercially available surfactants is ineffective. Lung transplantation has been successful, but the pretransplantation, transplantation, and posttransplantation medical and surgical care is highly specialized and available only at pediatric pulmonary transplantation centers; prompt recognition is critical if patients are to be considered for lung transplantation. Palliative care consultation is helpful.

No specific treatment is available for patients with lung disease caused by mutations in SFTPC or ABCA3. Therapeutic approaches used for interstitial lung diseases, such as the use of corticosteroids, quinolones, and macrolide antibiotics have been reported but not systematically evaluated. Infants with severe and progressive respiratory failure attributable to ABCA3 deficiency may be candidates for lung transplantation. The variable natural history of patients with SFTPC mutations and older children with ABCA3 deficiency makes predictions of prognosis difficult. Lung transplantation is reserved for patients with progressive and refractory respiratory failure who would otherwise qualify for transplantation irrespective of their diagnosis.

Treatment for patients with NKKX2-1 mutations is largely supportive. Hypothyroidism if present should be treated with thyroid replacement. Corticosteroids and other agents used for other types of surfactant dysfunction have not been formally evaluated. Some individuals have progressive lung disease, and lung transplantation has been performed for some subjects with end-stage lung disease. The variable progression of disease and presence of extrapulmonary disease may make evaluation and selection of subjects for transplantation particularly difficult.

Parents of children with surfactant dysfunction disorders should be offered genetic counseling. This allows for defining the recurrence risks for future pregnancies and the availability of antenatal diagnosis and therapeutic options, as well whether testing should be offered to other family members who may not be symptomatic.

Bibliography is available at Expert Consult.

405.2 Pulmonary Alveolar Proteinosis

Lawrence M. Nogee, F. Sessions Cole III, and Aaron Hamvas

Pulmonary alveolar proteinosis (PAP) is a rare type of diffuse lung disease characterized by the intraalveolar accumulation of pulmonary surfactant. Histopathologic examination shows distal air spaces to be filled with a granular, eosinophilic material that stains positively with periodic acid–Schiff reagent and is diastase resistant. This material contains large amounts of surfactant proteins and lipids and is the primary mechanism for its accumulation is impaired catabolism by alveolar macrophages. PAP has historically been classified as either primary (idiopathic) or secondary to a number of different conditions, although this terminology is evolving as specific etiologies for PAP are identified. (A fulminant, usually lethal form manifesting shortly after birth has been termed “congenital alveolar proteinosis,” but because this condition is caused by disrupted surfactant metabolism or surfactant dysfunction within alveolar type II cells, the disease is included under “Inherited Disorders of Surfactant Metabolism,” above (see Chapter 405.1).

ETIOLOGY AND PATHOPHYSIOLOGY

Disordered signaling of granulocyte macrophage colony-stimulating factor (GM-CSF) leading to impaired alveolar macrophage maturation is the major underlying cause of primary PAP in children and adults. Most cases of primary PAP in older children and adults are mediated by neutralizing autoantibodies directed against GM-CSF, which can be detected in serum and bronchoalveolar lavage (BAL) fluid. These autoantibodies block binding of GM-CSF to its receptor, thereby inhibiting alveolar macrophage maturation and function and surfactant clearance. Mutations in the genes encoding both the α and β subunits of the GM-CSF receptor (CSF2RA, CSF2RB) in children with primary alveolar proteinosis account for a genetic basis for some cases of primary PAP in childhood. Alveolar proteinosis has also been reported in children, including young infants, with lysinuric protein intolerance, a rare autosomal recessive disorder caused by mutations in the cationic amino acid transporter SLC7A7 (see Chapter 85.14). These children generally present with vomiting, hyperammonemia, and failure to thrive, although their pulmonary disease may prove fatal. Defective macrophage function has been demonstrated in lysinuric protein intolerance and a case of recurrence of the disease after lung transplantation also supports a primary role for alveolar macrophage dysfunction in the pathogenesis of PAP associated with lysinuric protein intolerance. PAP is also associated with some subtypes of Niemann-Pick disease (see Chapter 86.4).

Secondary alveolar proteinosis also may occur in association with infection, particularly in immunocompromised individuals. However, because the same pathologic process occurs in severely immunodeficient mice raised in a pathogen-free environment, it is not clear whether this phenotype results from a secondary infection or the underlying immunodeficiency. Environmental exposures to dust, silica, and chemicals and chemotherapeutic agents have also been associated with the development of secondary alveolar proteinosis.

CLINICAL MANIFESTATIONS

Infants and children with PAP present with dyspnea, fatigue, cough, weight loss, chest pain, or hemoptysis. In the later stages, cyanosis and digital clubbing may be seen. Pulmonary function changes include decreased diffusing capacity of carbon monoxide, lung volumes with a restrictive abnormality, and arterial blood gas values indicating marked hypoxemia and/or chronic respiratory acidosis. Alveolar proteinosis in infants and children is rare. Boys are affected 3 times as often as girls. Usually there is no identifiable etiologic factor (primary), although PAP may occur in association with malignancy or infection, particularly in the setting of systemic immunosuppression or congenital immunodeficiency, or following exposure to several inciting agents, such as dust and chemicals (secondary).

DIAGNOSIS

Histopathologic examination of lung biopsy specimens currently remains the gold standard for diagnosis of PAP in children, although this is likely to change as molecular tests become available. Immunochemical staining reveals abundant quantities of alveolar and intracellular surfactant proteins A, B, and D. Latex agglutination tests for the presence of anti-GM-CSF antibodies in BAL fluid or blood are highly sensitive and specific for the autoimmune forms of alveolar proteinosis. Elevations of GM-CSF in peripheral blood suggest a GM-CSF receptor defect, and molecular analysis of these genes should be pursued. The examination of sputum or BAL fluid for surfactant components has been used diagnostically in adults, but these methods have not been validated in children. Examination of peripheral blood and/or bone marrow for clonogenic stimulation of monocyte-macrophage precursors, GM-CSF receptor and ligand expression, and GM-CSF binding and signaling studies are available through research protocols.

TREATMENT

The natural history of primary PAP is highly variable, making prognostic and therapeutic decisions difficult. Total lung lavage has been associated with prolonged remissions of PAP in adults and remains a therapeutic option for patients with childhood PAP (Figs. 405-1 and 405-2). Younger infants with PAP may be more likely to have genetic mechanisms underlying their disease, and the role of repeated BAL in children has not been well studied, nor is it likely to be effective. It may provide a temporizing measure in some circumstances and may benefit patients with autoimmune or secondary PAP. Subcutaneous or inhaled administration of recombinant GM-CSF may improve pulmonary function in some adults with later-onset PAP. The role of exogenous GM-CSF treatment in children has not been well studied, although successful treatment has been reported in an adolescent with autoimmune-mediated PAP. Because children with GM-CSF receptor
Bibliography


defects generally have high serum levels of GM-CSF, exogenous GM-CSF seems unlikely to be effective in most such cases. Depending upon the nature of the mutation(s) responsible for the deficiency, some responsiveness of the receptor may be retained such that a response to exogenous GM-CSF is possible. As the primary defect for PAP resides in the alveolar macrophage, which is a bone marrow–derived cell, lung transplantation would not be expected to correct primary PAP.

Bibliography is available at Expert Consult.


Pulmonary hemorrhage may be characterized as focal or diffuse based on the site(s) of bleeding. A detailed review of pulmonary hemorrhage is in Chapter 407.2. The diagnosis of pulmonary hemosiderosis refers to the subset of patients with diffuse alveolar hemorrhage (DAH). Although the finding of pulmonary capillaritis is nonspecific with regard to underlying diagnosis, its presence appears to be an important negative prognostic factor in DAH and may indicate an underlying systemic vasculitic process or collagen vascular disease.

Disorders associated with pulmonary capillaritis may include systemic lupus erythematosus (SLE; see Chapter 158), drug-induced capillaritis, granulomatosis with polyangiitis (previously Wegener granulomatosis), Goodpasture syndrome, and Henoch-Schönlein purpura (see Chapter 167). The finding of DAH in patients with granulomatosis with polyangiitis and microscopic polyangiitis (MPA) (see Chapter 167) is frequently associated with pathologic evidence of pulmonary capillaritis. In patients with Goodpasture syndrome or SLE, DAH has been reported both with and without the associated finding of capillaritis. A number of systemic autoimmune and inflammatory disorders may predispose a host to DAH with pulmonary capillaritis. Similarly, a variety of drugs are associated with pulmonary capillaritis but the mechanisms here have not been identified.

These disorders are distinguished from those without pulmonary capillaritis. Those disorders in which the pathologic finding of capillary
Table 406-1  Diffuse Alveolar Hemorrhage Syndromes

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>SYNDROME</th>
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<tbody>
<tr>
<td>Disorders with pulmonary capillaritis</td>
<td>Idiopathic pulmonary capillaritis</td>
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<tr>
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<td>Granulomatosis with polyangiitis</td>
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<td>(Churg-Strauss syndrome)</td>
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</table>

| Disorders without pulmonary capillaritis: Noncardiovascular causes | Idiopathic pulmonary hemosiderosis |
| | Heiner syndrome |
| | Acute idiopathic pulmonary hemorrhage of infancy |
| | Bone marrow transplantation |
| | Immunodeficiency |
| | Coagulation disorders |
| | Hemolytic uremic syndromes |
| | Celiac disease (Lane-Hamilton syndrome) |
| | Infantilec (child abuse) |
| | Infection (HIV, cryptococcosis, Legionnaires disease) |

| Cardiovascular causes | Mitral stenosis |
| | Pulmonary venoocclusive disease |
| | Arteriovenous malformations |
| | Pulmonary lymphangioleiomyomatosis |
| | Pulmonary hypertension |
| | Pulmonary capillary hemangiomatosis |
| | Chronic heart failure |
| | Vascular thrombosis with infarction |


network disruption is absent are further divided into cardiac (pulmonary hypertension, mitral stenosis) and noncardiac (immunodeficiency, Heiner syndrome, coagulopathies, IPH) etiologies. A summary of the diagnoses that may manifest as recurrent or chronic pulmonary bleeding; Table 406-1 lists their classification.

**EPIDEMIOLOGY**

Disorders that present as DAH are highly variable in their severity, as well as in their associated symptomatology and identifiable abnormalities in laboratory testing; the diagnosis may be significantly delayed, making frequency estimates unreliable. Similarly, the prevalence of IPH is largely unknown. Among many children and young adults who were diagnosed with IPH in the past, the etiology of the hemorrhage might have been discovered if they had been studied with the newer and more advanced diagnostics available today; specific serologic testing has vastly improved our ability to appreciate immune mediated disease. Estimates of prevalence obtained from Swedish and Japanese retrospective case analyses vary from 0.24-1.23 cases per million. In retrospective case analyses vary from 0.24-1.23 cases per million. In nearly 80% of diagnosed cases the manifestations of IPH are seen before age 30 yr. The ratio of affected males: females is 1:1 in the childhood diagnosis group, and men are only slightly more affected in the group diagnosed as young adults.

**PATHOLOGY**

In pulmonary capillaritis, key histologic features include (1) fibrin thrombi, which occlude capillaries, (2) fibrin clots adherent to interalveolar septae, (3) fibrinoid necrosis of capillary walls, and (4) interstitial erythrocytes and hemosiderin. Illustrative but nonspecific pathologic findings, such as vascular smooth muscle hypertrophy (pulmonary hypertension), edema (mitral stenosis), or thrombosis (vascular thrombosis with infarction), may be found in those disorders that cause DAH without pulmonary capillaritis. The finding of blood in the airways or alveoli is representative of a recent hemorrhage. With repeated episodes of pulmonary hemorrhage, lung tissue appears brown secondary to this presence of hemosiderin. Hemosiderin-laden macrophages (HLMs) are seen with recovering, recurrent, or chronic pulmonary hemorrhage and are identifiable both in bronchoalveolar lavage fluid and in pathologic specimens of lung tissue. It takes 48-72 hr for the alveolar macrophages to convert iron from erythrocytes into hemosiderin. In a murine model, HLMs appear 3 days after a single episode of pulmonary hemorrhage and peak at 7-10 days. HLMs may be detectable for weeks to months after a hemorrhagic event. Other nonspecific pathologic findings include thickening of alveolar septa, g lobule cell hyperplasia, and hypertrophy of type II pneumocytes. Fibrosis may be seen with chronic disease.

**PATHOPHYSIOLOGY**

**Diffuse Alveolar Hemorrhage Associated with Pulmonary Capillaritis**

Granulomatosis with polyangiitis is a recognized etiology for DAH in children. This disease is classically characterized by necrotizing granuloma formation (with or without cavitation) of the upper and lower respiratory tract and by a necrotizing glomerulonephritis and small vessel vasculitis. In children, presentations attributable to the upper airway, including subglottic stenosis, may suggest the diagnosis.

The presence of antineutrophil cytoplasmic antibodies (ANCA) may be helpful in diagnosis and management, but the clinician must be aware that other ANCA-positive vasculitides, such as MPA and Churg-Strauss syndrome, may share this nonspecific laboratory finding. In small-vessel vasculitides, ANCA cause an inflammatory reaction that results in injury to the microvasculature. Antiproteinase-3 antibodies (cANCA) are classically associated with granulomatosis with polyangiitis whereas antimeylperoxidase antibodies (pANCA) are typically found in patients with MPA.

Patients with MPA (previously the microscopic variant of polyarteritis nodosa) demonstrate a systemic necrotizing vasculitis with a predilection for small vessels (venules, arterioles, capillaries) but without necrotizing granuloma formation. This diagnosis is precluded by the finding of immune complex deposition in order to differentiate MPA from other diseases (Henoch-Schönlein purpura, cryoglobulinemic vasculitis) that are associated with immune complex–mediated small-vessel vasculitis.

**Goodpasture syndrome** is an immune complex–mediated disease in which anti–glomerular basement membrane (GBM) antibody binds to the basement membrane of both the alveolus and the glomerulus. GBM antibodies attach to type IV collagen contained in the vascular endothelium. At the alveolar level, immunoglobulin (Ig) G, IgM, and complement are deposited at alveolar septa. Electron microscopy shows disruption of basement membranes and vascular integrity, which allows blood to escape into alveolar spaces.

Although alveolar hemorrhage is not commonly encountered in association with SLE, its occurrence is often severe and potentially life-threatening; mortality rates exceed 50%. Pathologic vasculitic features may be absent. Some immunofluorescent studies have revealed IgG and C3 deposits at the alveolar septa. However, a clear link between immune complex formation and alveolar hemorrhage has not been established.

In Henoch-Schönlein purpura, pulmonary hemorrhage is a rare but recognized complication. Pathologic findings have included transmural neutrophilic infiltration of small vessels, alveolar septal inflammation, and intra-alveolar hemorrhage. Vasculitis is the proposed mechanism for hemorrhage.

**Pulmonary renal syndromes** are defined as those where pulmonary and renal disease manifestations are predominant. These include the aforementioned granulomatosis with polyangiitis, Goodpasture...
Diffuse Alveolar Hemorrhage Not Associated with Pulmonary Capillaritis

A premature infant’s neonatal course can be complicated by pulmonary hemorrhage. The alveolar and vascular networks are immature and particularly prone to inflammation and damage by ventilator mechanics, oxidative stress, and infection. Pulmonary hemorrhage may be unrecognized if the volume of blood is insufficient to reach the proximal airways. The chest radiographic findings in pulmonary hemorrhage may be appreciated instead as a worsening picture of respiratory distress syndrome, edema, or infection.

Pulmonary hemosiderosis in association with cow’s milk hypersensitivity was first reported by Heiner in 1962. This condition is characterized by variable symptoms of milk intolerance. Symptoms can include grossly bloody or occult heme-positive stools, vomiting, failure to thrive, symptoms of gastroesophageal reflux, and/or upper airway congestion. Pathologic findings have included elevations of IgE and peripheral eosinophilia, as well as alveolar deposits of IgG, IgA, and C3. High titers to cow’s milk protein are also typically found in cow’s milk hypersensitivity. Association with pulmonary hemorrhage has remained controversial but multiple case series have provided support for the anecdotal association. In one series, infants presenting with recurrent respiratory symptoms and iron-deficiency anemia; all infants improved with elimination of cow’s milk from their diets and a subset thereafter had a recurrence of pulmonary disease with a cow’s milk challenge. However, many patients with milk precipitants did not have symptoms of hemosiderosis and patients with hemosiderosis did not always have milk precipitins; the relationship may be an association rather than causal in nature.

A number of case reports and case series have suggested an association between celiac disease (see Chapter 338.2) and DAH. In these reports, a resolution of intestinal and pulmonary symptoms along with resolution of radiographic disease has been seen after the adoption of a gluten-free diet. Consideration of testing for celiac disease in those patients with pulmonary hemorrhage and suggestive gastrointestinal symptomatology is suggested.

A number of additional associated conditions and exposures exist as causes for DAH. These are typically noninflammatory in nature and may be diversely attributable to cardiac, vascular, lymphatic or hematologic etiologies. Graft-versus-host disease has been implicated in transplant recipients and DAH may rarely be attributable to nonaccidental trauma. These etiologies for DAH occur relatively infrequently in the pediatric population, and suggested mechanisms for hemorrhage are variable.

The diagnosis of IPH is a diagnosis of exclusion and is only made when there is evidence of chronic or recurrent DAH and when exhaustive evaluations for primary or secondary etiologies have negative results. Renal and systemic involvement should be absent and a biopsy specimen should not reveal any evidence of granulomatous disease, vasculitis, infection, infarction, immune complex deposition or malignancy. Some patients initially diagnosed with IPH will later be found to have Goodpasture syndrome, SLE, or MPA; therefore, some cases of IPH may represent unrecognized immune-mediated disorders.

CLINICAL MANIFESTATIONS

The clinical presentation of pulmonary hemosiderosis is highly variable. In most symptomatic cases, DAH is heralded by symptoms of hemosiderosis and dyspnea with associated hypoxemia and the finding of alveolar infiltration on chest radiograph. The diagnosis may be problematic as young children often lack the ability to effectively expectorate and may not present with hemosiderosis. As the presence of blood in the lung is a trigger for airway irritation and inflammation, the patient may present after an episode of hemorrhage with wheezing, cough, dyspnea, and alterations in gas exchange, reflecting bronchospasm, edema, mucus plugging, and inflammation; this presentation may result in an incorrect diagnosis of asthma or bronchiolitis. A lack of pulmonary symptoms does not preclude the diagnosis of DAH and children may present only with chronic fatigue or pallor.

Symptoms may reflect an underlying and associated disease process rather than specifically related to pulmonary hemorrhage. Presentations can vary widely from a relative lack of symptoms to shock or sudden death. Bleeding may occasionally be recognized from the presence of alveolar infiltrates on a chest radiograph alone. It should be noted, however, that the absence of an infiltrate does not rule out an ongoing hemorrhagic process.

On physical examination, the patient may be pale with tachycardia and tachypnea. During an acute exacerbation, children are frequently febrile. Examination of the chest may reveal retractions and differential or decreased aeration, with crackles or wheezes. The patient may present in shock with respiratory failure from massive hemoptysis. Children in particular may present with symptoms of chronic anemia, such as failure to thrive.

LABORATORY FINDINGS AND DIAGNOSIS

Pulmonary hemorrhage is classically associated with a microcytic, hypochromic anemia. Reductions of serum iron levels, decreased or normal total iron-binding capacity and normal to increased ferritin levels may be found with chronic disease. An elevated erythrocyte sedimentation rate is a nonspecific finding. The reticulocyte count is frequently elevated. Patients with pulmonary capillaritis have lower hematocrits and higher erythrocyte sedimentation rates. The anemia of IPH can mimic a hemolytic anemia. Elevations of plasma bilirubin are caused by absorption and breakdown of hemoglobin in the alveoli. Any or all of these hematologic manifestations may be absent in the presence of recent hemoptysis.

White blood cell count and differential should be evaluated for evidence of infection and eosinophilia. A peripheral smear and direct Coombs test may suggest a vasculitic process. A stool specimen positive for occult blood may suggest associated gastrointestinal disease but can also reflect swallowed blood. Renal and liver functions should be reviewed. A urinalysis should be obtained to assess for evidence of a pulmonary–renal syndrome. A coagulation profile, quantitative immunoglobulins (including IgE), and complement studies are recommended. Testing for von Willebrand disease is also indicated.

Testing for ANCA (cANCA, pANCA), antinuclear antibody, double-stranded DNA, rheumatoid factor, antiphospholipid antibody, and GBM antibody evaluates for a number of immune-mediated and vasculitic processes that may be associated with pulmonary capillaritis.

Sputum or pulmonary secretions should be analyzed for granulomas and acid-fast bacilli. A sputum Gram stain may be diagnostic for atypical pneumonitis. Cultures for acid-fast bacilli and fungi should be performed. Testing for the presence of recent hemorrhage. Any or all of these hematologic manifestations may be absent in the presence of recent hemoptysis.

Chest x-rays may reveal evidence of acute or chronic disease. Hyperinflation is frequently seen, especially during an acute hemorrhage. Infiltrates are typically symmetric and may spare the apices of the lung. Consolidation may also be visible. With chronic disease, fibrosis, lymphadenopathy and nodularity may be seen. CT findings may demonstrate a subclinical and contributory disease process. The presence of a cardiac murmur, cardiomegaly on X-ray or a clinical suspicion for left-sided heart lesion suggests the need for a complete cardiac evaluation, including electrocardiogram and echocardiogram.

Pulmonary function testing will likely reveal primarily obstructive disease in the acute period. With more chronic disease, fibrosis and restrictive disease tend to predominate. Oxygen saturation levels may be decreased. Lung volumes may reveal air trapping acutely and decreases in total lung capacity chronically. The diffusing capacity of carbon monoxide may be low or normal in the chronic phase
but is likely to be elevated in the setting of an acute hemorrhage, because carbon monoxide binds to the hemoglobin in extravasated red blood cells.

Lung biopsy is warranted when DAH occurs without discernible etiology, extrapulmonary disease, or circulating GBM antibodies. When obtained, pulmonary tissue should be evaluated for evidence of vasculitis, immune complex deposition, and granulomatous disease.

Many have supported a diagnosis of IPH without lung biopsy if the patient has a typical presentation with diffuse infiltration on radiography, anemia, HLMs in bronchoalveolar lavage, sputum or gastric aspirate, absence of systemic disease and negative serology for immune-mediated disease. However, a number of patients meeting these criteria have been proven to have pulmonary capillaritis on review of pathologic lung tissue specimens. Therefore, a lung biopsy is recommended in any child presenting with DAH of uncertain etiology.

TREATMENT
Supportive therapy, including volume resuscitation, ventilatory support, supplemental oxygen, and transfusion of blood products, may be warranted in the patient with pulmonary hemosiderosis. Surgical or medical therapy should be directed at any treatable underlying condition. In IPH, systemic corticosteroids are frequently utilized as first-line treatment and are expected to be of particular benefit in the setting of immune-mediated disease. Steroids modulate neutrophil influx and the inflammation associated with hemorrhage; consequently, they may decrease progression toward fibrotic disease.

Treatment may be provided in the form of methylprednisolone 2-4 mg/kg/day divided every 6 hr or in the form of prednisone 0.5-1 mg/kg daily and decreased to every-other-day after resolution of acute symptoms. Successful treatment is also associated with the use of pulse steroid therapy; methylprednisolone may be given at a dose of 10-30 mg/kg (maximum 1 g) infused over 1 hr for 3 consecutive days and repeated monthly. Early treatment with corticosteroids appears to decrease episodes of hemorrhage. Steroid therapy is associated with improved survival and may be tapered as tolerated with disease remission or chronically maintained.

Steroid-sparing agents, including cyclophosphamide, azathioprine, hydroxychloroquine, methotrexate, and intravenous immunoglobulin, have been successfully used as adjunctive therapy in patients with chronic, unremitting or recurrent hemorrhage. Maintenance therapy with 6-mercaptopurine may produce favorable results in achieving long-term remission. The potential adverse effects of these pharmacologic interventions should be recognized and treated patients must be closely monitored for drug-related complications. Cushing syndrome is a well-recognized complication of chronic steroid therapy. Thrombocytopenia in association with low-dose cyclophosphamide has also been reported. Chronically immunosuppressed patients are at risk for opportunistic infection; *Legionella* pneumonia infection has been described in a survivor of IPH.

Plasmapheresis is a recognized therapy for anti-GBM antibody disease. Intravenous immunoglobulin has been used in immune complex–mediated disease.

In chronic disease, progression to debilitating pulmonary fibrosis has been described. Lung transplantation has been performed in patients with IPH refractory to immunosuppressive therapy. In one reported case study, IPH recurred in the transplanted lung.

PROGNOSIS
The outcome of patients suffering from DAH is largely dependent on the underlying disease process. Some conditions respond well to immunosuppressive therapies and remissions of disease are well documented. Other syndromes, especially those associated with pulmonary capillaritis, carry a poorer prognosis. In IPH, mortality is usually attributable to massive hemorrhage or, alternatively, to progressive fibrosis, respiratory insufficiency, and right-sided heart failure.

Long-term prognosis in patients with IPH varies among studies. Initial case study reviews suggested an average survival after symptom onset of only 2.5 yr. In this early review, a minority of patients were treated with steroids. Recent reviews have demonstrated vastly improved 5yr (86%) and 8 yr (93%) survival in association with the use of immunosuppressive therapies. To date, specific immunosuppressive treatment regimens have not been studied in a prospective manner.

*Bibliography is available at Expert Consult.*
Bibliography


Venous thromboembolic disease (VTE) has become an increasingly recognized critical problem in children and adolescents with chronic disease, as well as in those patients without identifiable risk factors (Table 407-1). Improvements in survival with chronic illness have likely contributed to the larger number of children presenting with these thromboembolic events; they are a significant source of morbidity and mortality and may only be recognized on post mortem examination. A high level of clinical suspicion and appropriate identification of at-risk individuals is therefore recommended.

ETIOLOGY

No single classification scheme exists for the etiology of VTE. A number of risk factors may be identified in children and adolescents; the presence of immobility, malignancy, pregnancy, infection, indwelling central venous catheters and a number of inherited and acquired thrombophilic conditions have all been identified as placing an individual at risk. In children, a significantly greater percentage of VTEs are risk associated as compared with their adult counterparts. Children with deep venous thrombosis (DVT) and pulmonary embolism (PE) are much more likely to have 1 or more identifiable conditions or circumstances placing them at risk. In a retrospective cohort of patients with VTE in U.S. children’s hospitals from 2001-2007, the majority (63%) of affected children were found to have 1 or more chronic medical comorbidities. In a large Canadian registry, 96% of pediatric patients were found to have 1 risk factor and 90% had 2 or more risk factors. In contrast, approximately 60% of adults with this disorder have an identifiable risk factor (see Table 407-1).

Embolic disease in children is varied in its origin. An embolus can contain thrombus, air, amniotic fluid, septic material, or metastatic neoplastic tissue. Thromboemboli are the type most commonly encountered. A commonly encountered risk factor for DVT and PE in the pediatric population is the presence of a central venous catheter. More than 50% of DVTs in children and more than 80% in newborns are found in patients with indwelling central venous lines. The presence of a catheter in a vessel lumen, as well as instilled medications, can induce endothelial damage and favor thrombus formation.

Children with malignancies are also at considerable risk. Although PE has been described in children with leukemia, the risk of PE is more significant in children with solid rather than hematologic malignancies. A child with malignancy may have numerous risk factors related to the primary disease process and the therapeutic interventions. Infection from chronic immunosuppression may interact with hypercoagulability of malignancy and chemotherapeutic effects on the endothelium.
Part XIX ♦ Respiratory System

Table 407-1 | Risk Factors for Pulmonary Embolism

<table>
<thead>
<tr>
<th>ENVIRONMENTAL</th>
<th>Long-haul air travel</th>
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<tr>
<td></td>
<td>Obesity</td>
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<td></td>
<td>Cigarette smoking</td>
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<tr>
<td></td>
<td>Hypertension</td>
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<td></td>
<td>Immobility</td>
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<tr>
<th>WOMEN’S HEALTH</th>
<th>Oral contraceptives, including progesterone-only and, especially, third-generation pills</th>
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<tbody>
<tr>
<td></td>
<td>Pregnancy</td>
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<td></td>
<td>Hormone replacement therapy</td>
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<td>Septic abortion</td>
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<tr>
<th>MEDICAL ILLNESS</th>
<th>Previous pulmonary embolism or deep venous thrombosis</th>
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<tr>
<td></td>
<td>Cancer</td>
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<td></td>
<td>Heart failure</td>
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<td></td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td></td>
<td>Diabetes mellitus</td>
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<td></td>
<td>Inflammatory bowel disease</td>
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<td></td>
<td>Antipsychotic drug use</td>
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<td></td>
<td>Long-term indwelling central venous catheter</td>
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<td></td>
<td>Permanent pacemaker</td>
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<td></td>
<td>Internal cardiac defibrillator</td>
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<td>Stroke with limb paresis</td>
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<td></td>
<td>Spinal cord injury</td>
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<td></td>
<td>Nursing home confinement or current or repeated hospital admission</td>
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<thead>
<tr>
<th>SURGICAL</th>
<th>Trauma</th>
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<tbody>
<tr>
<td></td>
<td>Orthopedic surgery</td>
</tr>
<tr>
<td></td>
<td>General surgery</td>
</tr>
<tr>
<td></td>
<td>Neurosurgery, especially craniotomy for brain tumor</td>
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<table>
<thead>
<tr>
<th>THROMBOPHILIA</th>
<th>Factor V Leiden mutation</th>
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<tbody>
<tr>
<td></td>
<td>Prothrombin gene mutation</td>
</tr>
<tr>
<td></td>
<td>Hyperhomocysteinanemia (including mutation in methylenetetrahydrofolate reductase)</td>
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<tr>
<td></td>
<td>Antiphospholipid antibody syndrome</td>
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<tr>
<td></td>
<td>Deficiency of antithrombin III, protein C, or protein S</td>
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<tr>
<td></td>
<td>High concentrations of factor VIII or XI</td>
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<tr>
<td></td>
<td>Increased lipoprotein A</td>
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<table>
<thead>
<tr>
<th>NONTHROMBOTIC</th>
<th>Air</th>
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<tbody>
<tr>
<td></td>
<td>Foreign particles (e.g., hair, talc, as a consequence of intravenous drug misuse)</td>
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<tr>
<td></td>
<td>Amniotic fluid</td>
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<tr>
<td></td>
<td>Bone fragments, bone marrow</td>
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<tr>
<td></td>
<td>Fat</td>
</tr>
<tr>
<td></td>
<td>Tumors (Wilms tumor)</td>
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In a retrospective cohort of patients with VTE from 2001-2007, pediatric malignancy was the medical condition most strongly associated with recurrent VTE.

In the neonatal period, thromboembolic disease and PE may be related to indwelling catheters used for parenteral nutrition and medication delivery. Pulmonary thromboemboli in neonates generally occurs as a complication of underlying disease; the most common associated diagnosis is congenital heart disease but sepsis and birth asphyxia are also notable associated conditions. Other risk factors include a relative immaturity of newborn infants’ coagulation; plasma concentrations of vitamin K–dependent coagulation factors (II, VII, IX, X); factors XII, XI, and prekallikrein and high-molecular-weight kininogen are only approximately half of adult levels (see Chapter 475). PE in neonates may occasionally reflect maternal risk factors, such as diabetes and toxemia of pregnancy. Infants with congenitally acquired homozygous deficiencies of antithrombin, protein C, and protein S are also more likely to present with thromboembolic disease in the neonatal period (see Chapter 478).

Pulmonary air embolism is a defined entity in the newborn or young infant and is attributed to the conventional ventilation of critically ill (and generally premature) infants with severe pulmonary disease. In the majority of instances, the pulmonary air embolism is preceded by an air-leak syndrome. Infants may become symptomatic and critically compromised by as little as 0.4 mL/kg of intravascular air; these physiologic derangements are thought to be secondary to the effects of nitrogen.

Prothrombotic disease can also manifest in older infants and children. Disease can be congenital or acquired. Inherited thrombophilic conditions include deficiencies of antithrombin, protein C, and protein S, as well as mutations of factor V Leiden (G1691A) (see Chapter 478) and prothrombin (factor II 20210A mutation) (see Chapter 478), and elevated values of lipoprotein A. In addition, multiple acquired thrombotic conditions exist; these include the presence of lupus anticoagulant (may be present without the diagnosis of systemic lupus erythematosus), anticardiolipin antibody, and anti–β2-glycoprotein 1 antibody. Finally, conditions such as hyperhomocysteinemia (see Chapter 86) may have both heritable and dietary determinants. All have all been linked to thromboembolic disease. DVT/PE may be the initial presentation.

Children with sickle cell disease are also at high risk for pulmonary embolus and infarction. Acquired prothrombotic disease is seen in conditions such as nephrotic syndrome (see Chapter 527) and antiphospholipid antibody syndrome. From one-quarter to one-half of children with systemic lupus erythematosus (see Chapter 158) have thromboembolic disease. There is a significant association with VTE onset in children for each inherited thrombophilic trait evaluated, thereby illuminating the importance of screening for thrombophilic conditions for those at risk for VTE.

Other risk factors include infection, cardiac disease, recent surgery, and trauma. Surgical risk is thought to be more significant when immobility will be a prominent feature of the recovery. Use of oral contraceptives confers additional risk, although the level of risk in patients taking these medications appears to be decreasing, perhaps as a result of the lower amounts of estrogen in current formulations.

Septic emboli are rare in children but may be caused by osteomyelitis, jugular vein or umbilical thrombophlebitis, cellulitis, urinary tract infection, and right-sided endocarditis.

EPIDEMIOLOGY

A retrospective cohort study was performed with patients younger than 18 yr of age, discharged from 35-40 children’s hospitals across the United States from 2001-2007. During this time, a dramatic increase was noted in the incidence of VTE; the annual rate of VTE increased by 70% from 34 to 58 cases per 10,000 hospital admissions. Although this increased incidence was noted in all age groups, a bimodal distribution of patient ages was found, consistent with prior studies; infants younger than 1 yr of age and adolescents made up the majority of admissions with VTE, but neonates continue to be at greatest risk. The peak incidence for VTE in childhood appears to occur in the 1st mo of life. It is in this neonatal period that thromboembolic events are more problematic, likely as a result of an imbalance between procoagulant factors and fibrinolysis. According to a 2013 update by Nowak-Göttli et al, the yearly incidence of venous events was estimated at 5.3 per 10,000 hospital admissions in children and 24 per 10,000 in the neonatal intensive care.

Pediatric autopsy reviews have estimated the incidence of thromboembolic disease in children as between 1% and 4%, although not all were clinically significant. Thromboembolic pulmonary disease is often unrecognized, and antemortem studies may underestimate the true incidence. Pediatric deaths from isolated pulmonary emboli are rare. Most thromboemboli are related to central venous catheters. The source of the emboli may be lower or upper extremity veins as well as the pelvis and right heart. In adults, the most common location for DVT
is the lower leg. However, one of the largest pediatric VTE/PE registries found two-thirds of DVTs occurring in the upper extremity.

**PATHOPHYSIOLOGY**

Favorable conditions for thrombus formation include injury to the vessel endothelium, hemostasis, and hypercoagulability. In the case of PE, a thrombus is dislodged from a vein, travels through the right atrium and lodges within the pulmonary arteries. In children, emboli that obstruct <50% of the pulmonary circulation are generally clinically silent unless there is significant coexistent cardiopulmonary disease. In severe disease, right ventricular afterload is increased with resultant right ventricular dilation and increases in right ventricular and pulmonary arterial pressures. In severe cases, a reduction of cardiac output and hypotension may result from concomitant decreases in left ventricular filling. In rare instances of death from massive pulmonary embolus, marked increases in pulmonary vascular resistance and heart failure are usually present.

Arterial hypoxemia results from unequal ventilation and perfusion; the occlusion of the involved vessel prevents perfusion of distal alveolar units, thereby creating an increase in dead space and hypoxia with an elevated alveolar–arterial oxygen tension difference (see Chapter 373). Most patients are hypocarbar secondry to hyperventilation, which often persists even when oxygenation is optimized. Abnormalities of oxygenation and ventilation are likely to be less significant in the pediatric population, possibly owing to less underlying cardiopulmonary disease and greater reserve. The vascular supply to lung tissue is abundant, and pulmonary infarction is unusual with pulmonary embolus but may result from distal arterial occlusion and alveolar hemorrhage.

**CLINICAL MANIFESTATIONS**

Presentation is variable, and many pulmonary emboli are silent. Rarely, a massive PE may manifest as cardiopulmonary failure. Children are more likely to have underlying disease processes or risk factors but might still present asymptomatically with small emboli. Common symptoms and signs of PE caused by larger emboli include hypoxia (cyanosis), dyspnea, cough, pleuritic chest pain, and hemoptyis. Pleuritis chest pain is the most common presenting symptom in adolescents (84%), whereas unexplained and persistent tachypnea may suggest PE in all pediatric patients. Localized crackles may occasionally be appreciated on examination. A high level of clinical suspicion is required because a variety of diagnoses may cause similar symptoms; nonspecific complaints may frequently be attributed to an underlying disease process or an unrelated/incorrect diagnosis. Confirmatory testing should follow a clinical suspicion for PE. In adults, clinical prediction rules have been published and are based on risk factors, clinical signs, and symptoms. No such clinical prediction rules have been validated in the pediatric population.

**LABORATORY FINDINGS AND DIAGNOSIS**

The electrocardiogram, arterial blood gas, and chest radiograph may be utilized to rule out contributing or comorbid disease but are not specific or specific in the diagnosis of PE. Electrocardiographs may reveal ST-segment changes or evidence of pulmonary hypertension with right ventricular failure (cor pulmonale); such changes are nonspecific and nondiagnostic. Radiographic images of the chest are often normal in a child with PE and any abnormalities are likely to be nonspecific. Patients with septic emboli may have multiple areas of nodularity and cavitation, which are typically located peripherally in both lung fields. Many patients with PE have hypoxemia. The alveolar–arterial oxygen tension difference gradient is more sensitive in detecting gas exchange derangements.

A review of results of a complete blood count, urinalysis, and coagulation profile is warranted. Prothrombotic diseases should be highly suspected on the basis of past medical or family history; additional laboratory evaluations include fibrinogen assays, protein C, protein S, and antithrombin III studies, and analysis for factor V Leiden mutation, as well as evaluation for lupus anticoagulant and anticardiolipin antibodies. Echocardiograms may be warranted to assess ventricular size and function. An echocardiogram is required if there is any suspicion of intracardiac thrombi or endocarditis.

Noninvasive venous ultrasound testing with Doppler flow can be used to confirm DVT in the lower extremities; ultrasonography may not detect thrombi in the upper extremities or pelvis (Fig. 407-1A). In patients with significant venous thrombosis, D dimers are usually elevated. It is a sensitive but nonspecific test for venous thrombosis. The D dimer may not be clinically relevant in the children with PE as this group is more likely to have an underlying comorbid condition that is also associated with an increased level of D dimers. When a high level of suspicion exists, confirmatory testing with venography should be pursued. DVT can be recurrent and multifocal and may lead to repeated episodes of PE.

Although a ventilation–perfusion (V–Q) radionuclide scan is a noninvasive and potentially sensitive method of pulmonary embolus detection, the interpretation of V–Q scans can be problematic. Helical or spiral CT with an intravenous contrast agent is valuable and the diagnostic test of choice to detect a PE (see Fig. 407-1B). CT studies detect emboli in lobar and segmental vessels with acceptable sensitivities. Poorer sensitivities may be encountered in the evaluation of the subsegmental pulmonary vasculature. Pulmonary angiography is the
gold standard for diagnosis of PE, but with current availability of multidetector spiral CT angiography, it is not necessary except in unusual cases.

MRI may be emerging as a diagnostic option for patients with VTE. The accuracy of this method is similar to that of multidetector CT. It may be preferable in patients with allergic reactions to contrast material and in pediatric patients in whom the risk of early exposure to ionizing radiation has been established.

**TREATMENT**

Initial treatment should always be directed toward stabilization of the patient. Careful approaches to ventilation, fluid resuscitation, and isotropic support are always indicated, because improvement in 1 area of decompensation can often exacerbate coexisting pathology.

After the patient with a PE has been stabilized, the next therapeutic step is anticoagulation. Evaluations for prothrombotic disease must precede anticoagulation. Acute-phase anticoagulation therapy may be provided with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Heparin acts by enhancing the activity of antithrombin. LMWH is generally preferred in children; this drug can be administered subcutaneously and the need for serum monitoring is decreased. The risk of heparin-induced thrombocytopenia is also decreased with LMWH as compared to UFH. Alternatively, UFH is preferred with patients who have an elevated risk of bleeding as UFH has a shorter half-life than LMWH. UFH is also used preferentially in patients with compromised renal function. In monitoring of drug levels, laboratories must be aware of the drug chosen in order to use the appropriate assay. For UFH, the therapeutic range is 0.3-0.7 anti-Xa activity units/mL. In LMWH, the therapeutic range is 0.5-1.0 units/mL. When the anti-Xa assay is not available, the activated partial thromboplastin time may be used with a goal of 60-85 sec or approximately 1.5-2 times the upper limit of age appropriate normal values. The recommended duration of heparinization during acute treatment is 5-10 days; this length of therapy has been extrapolated from adult data. Long-term therapy with heparin should be avoided whenever possible. Side effects include the aforementioned heparin-induced thrombocytopenia as well as bleeding and osteoporosis.

Extension of anticoagulation therapy occurs in the subacute phase and may utilize LMWH or warfarin. Warfarin is generally initiated after establishing effective anticoagulation with heparin because severe congenital deficiencies of protein C may be associated with warfarin skin necrosis. The starting dose for warfarin in children is generally 0.1 mg/kg orally administered once daily. Monitoring is via the international normalized ratio (INR) and the therapeutic INR range for warfarin therapy in VTE is 2.0-3.0. The INR is generally monitored 5 days after initiating therapy or a similar period after dose changes and weekly thereafter until stable. The INR should be obtained with any evidence of abnormal bleeding and should be discontinued at least 5 days prior to invasive procedures. The utilization of an anticoagulation team and/or established treatment algorithms is recommended in order to optimize patient safety. With a first occurrence of VTE, anti-coagulation is recommended for 3-6 mo in the setting of an identifiable, reversible, and resolved risk factor (e.g., postoperative state). Longer treatment is indicated in patients with idiopathic VTE (6-12 mo) and in those with chronic clinical risk factors (12 mo-lifelong). In the setting of a congenital thrombophilic condition, the duration of therapy is often indefinite.

Inhibitors of factor Xa (rivaroxaban, etc.) may become an alternate therapy for both acute PE and long-term treatment.

Thrombolytic agents such as recombinant tissue plasminogen activator, may be utilized in combination with anticoagulants in the early stages of treatment; their use is most likely to be considered in children with hemodynamically significant PE (echocardiogram evidence of right ventricular dysfunction) or other severe potential clinical sequelae of VTE. Combined therapy may reduce the incidences of progressive thromboembolism, pulmonary embolus, and post-thrombotic syndrome. Mortality rate appears to be unaffected by additional therapies; nonetheless, the additional theoretic risk of hemorrhage limits the use of combination therapy in all but the most compromised patients. The use of thrombolytic agents in patients with active bleeding, recent cerebrovascular accidents, or trauma is contraindicated.

Surgical embolectomy is invasive and is associated with significant mortality. Its application should be limited to those with persistent hemodynamic compromise refractory to standard therapy.

**PROGNOSIS**

Mortality in pediatric patients with PE is likely to be attributable to an underlying disease process rather than to the embolus itself. Short-term complications include major hemorrhage (either due to the thrombosis or secondary to anticoagulation). Conditions associated with a poorer prognosis include malignancy, infection, and cardiac disease. The mortality rate in children from PE is 2.2%. Recurrent thromboembolic disease may complicate recovery. The practitioner must conduct an extensive evaluation for underlying pathology so as to prevent progressive disease. Postthrombotic syndrome is another recognized complication of pediatric thrombotic disease. Venous valvular damage can be initiated by the presence of DVT, leading to persistent venous hypertension with ambulation and valvular reflux. Symptoms include edema, pain, increases in pigmentation, and ulcerations. Affected pediatric patients may suffer lifelong disability.

*Bibliography is available at Expert Consult.*

### 407.2 Pulmonary Hemorrhage and Hemoptysis

*Mary A. Nevin*

Pulmonary hemorrhage is relatively uncommon but a potentially fatal occurrence in children. The patient with suspected hemoptysis may present acutely or subacutely and to a variety of different practitioners with distinct areas of specialty. Diffuse, slow bleeding in the lower airways may become severe and manifest as anemia, fatigue, or respiratory compromise without the patient ever experiencing episodes of hemoptysis. Hemoptysis must also be separated from episodes of hematemesis or epistaxis, each of which may have indistinguishable presentations in the young patient.

**ETIOLOGY**

Tables 407.2 and 406-1 (in Chapter 406) present conditions that can manifest as pulmonary hemorrhage or hemoptysis in children. The chronic (opposed to an acute) presence of a foreign body can lead to inflammation and/or infection, thereby inducing hemorrhage. Bleeding is more likely to occur in association with a chronically retained foreign body of vegetable origin.

Hemorrhage most commonly reflects chronic inflammation and infection such as that seen with bronchiectasis due to cystic fibrosis or with cavitary disease in association with infectious tuberculosi. Hemoptysis may occasionally reflect an acute and intense infectious condition such as bronchitis or bronchopneumonia.

Other relatively common etiologies are congenital heart disease and trauma. Pulmonary hypertension secondary to cardiac disease is a prominent etiology for hemoptysis in those patients without cystic fibrosis. Traumatic irritation or damage in the airway may be accidental in nature. Traumatic injury to the airway and pulmonary contusion may result from motor vehicle crashes or other direct force injuries. Bleeding can also be related to instrumentation or iatrogenic irritation of the airway as is commonly seen in a child with a tracheostomy or a child with repeated suction trauma to the upper airway. Children who have been victims of nonaccidental trauma or deliberate suffocation can also be found to have blood in the mouth or airway (see Chapter 40). Fictitious hemoptysis may rarely be encountered in the setting of Factitious Disorder by Proxy (formerly Munchausen’s by proxy; see Chapter 40.2).
Bibliography


Rare causes for hemoptysis include tumors and vascular anomalies such as arteriovenous malformations (Fig. 407-2). Congenital vascular malformations in the lung may also be associated with hereditary hemorrhagic telangiectasia. Tumors must be cautiously investigated when encountered with a flexible fiberoptic bronchoscope as bleeding may be massive and difficult to control.

Syndromes associated with vasculitic, autoimmune, and idiopathic disorders can be associated with diffuse alveolar hemorrhage (see Chapter 406).

Acute idiopathic pulmonary hemorrhage of infancy is a distinct entity and is described as an episode of pulmonary hemorrhage in a previously healthy infant born at greater than 32 wk of gestation and whose age is less than 1 yr with the following: (1) abrupt or sudden onset of overt bleeding or frank evidence of blood in the airway, (2) severe presentation leading to acute respiratory distress or failure and requiring intensive care and invasive ventilatory support, and (3) diffuse bilateral infiltration on chest radiographs or computed tomography. Prior suggestions of an association between acute idiopathic pulmonary hemorrhage of infancy and toxic mold exposure have not been supported on subsequent review.

**EPIDEMIOLOGY**

The frequency with which pulmonary hemorrhage occurs in the pediatric population is difficult to define. This difficulty is largely related to the variability in disease presentation. Chronic bronchiectasis as seen in cystic fibrosis (see Chapter 403) or ciliary dyskinesia (see Chapter 404) can cause hemoptysis, but usually occurs in children older than 10 yr of age. The incidence of pulmonary hemorrhage may be significantly underestimated because many children and young adults swallow rather than expectorate mucus, a behavior that may prevent recognition of hemoptysis, the primary presenting symptom of the disorder.

**PATHOPHYSIOLOGY**

Pulmonary hemorrhage can be localized or diffuse. Focal hemorrhage from an isolated bronchial lesion is often secondary to infection or chronic inflammation. Erosion through a chronically inflamed airway into the adjacent bronchial artery is a mechanism for potentially massive hemorrhage. Bleeding from such a lesion is more likely to be bright red, brisk, and secondary to enlarged bronchial arteries and systemic arterial pressures. The severity of more diffuse hemorrhage can be difficult to ascertain. The rate of blood loss may be insufficient to reach the proximal airways. Therefore, the patient may present without hemoptysis. The diagnosis of pulmonary hemorrhage is generally achieved by finding evidence of blood or hemosiderin in the lung. Within 48-72 hr of an episode of bleeding, alveolar macrophages convert the iron from erythrocytes into hemosiderin. It may take weeks to clear these hemosiderin-laden macrophages completely from the alveolar spaces. This fact may allow differentiation between acute and chronic hemorrhage. Hemorrhage is often followed by the influx of neutrophils and other proinflammatory mediators. With repeated or chronic hemorrhage, pulmonary fibrosis can become a prominent pathologic finding.

**CLINICAL MANIFESTATIONS**

The severity of presentation in patients with hemoptysis and pulmonary hemorrhage is highly variable. Older children and young adults with a focal hemorrhage may complain of warmth or a “bubbling” sensation in the chest wall. This can occasionally aid the clinician in locating the area involved. Rapid and large-volume blood loss manifests as symptoms of cyanosis, respiratory distress, and shock. Chronic, subclinical blood loss may manifest as anemia, fatigue, dyspnea, or altered activity tolerance. Less commonly, patients present with persistent infiltrates on chest radiograph or symptoms of chronic illness such as failure to thrive.

Pulmonary arteriovenous malformations may present with hemoptysis, hemotherax, a round localized mass on x-ray or CT, clubbing, cyanosis, or embolic phenomenon.

**LABORATORY FINDINGS AND DIAGNOSIS**

A patient with suspected hemorrhage should have a laboratory evaluation with complete blood count and coagulation studies. The complete blood count result may demonstrate a microcytic, hypochromic anemia but may be normal early in an acute bleeding episode. If iron stores are sufficient, a reticulocytosis may be present. Other laboratory findings are highly dependent on the underlying diagnosis. A urinalysis may show evidence of nephritis in patients with a comorbid pulmonary renal syndrome. The classic and definitive finding in pulmonary hemorrhage is that of hemosiderin-laden macrophages in pulmonary secretions. Hemosiderin-laden macrophages may be detected by sputum analysis with Prussian blue staining when a patient is able to successfully expectorate sputum from the lower airways. In younger children, or in weak or neurodevelopmentally compromised patients unable to expectorate sputum, induced sputum may provide an acceptable specimen; alternatively, a flexible bronchoscopy with bronchoalveolar lavage may be required for specimen retrieval.

Chest radiographs may demonstrate fluffy bilateral densities, as seen in acute idiopathic pulmonary hemorrhage of infancy (Fig. 407-3) or the patchy consolidation seen in idiopathic pulmonary hemosiderosis (Fig. 407-4). Alveolar infiltrates seen on chest radiograph may be regarded as a representation of recent bleeding, but their absence does not rule out the occurrence of pulmonary hemorrhage. Infiltrates, when present, are often symmetric and diffuse and may be preferentially located in the perihilar regions and lower lobes. The costophrenic angles and lung apices are frequently spared. CT may be indicated to assess for underlying disease processes.
Lung biopsy is rarely necessary unless bleeding is chronic or an etiology cannot be determined with other methods. Pulmonary function testing, including a determination of gas exchange, is important to assess the severity of the ventilatory defect. In older children, spirometry may demonstrate evidence of predominantly obstructive disease in the acute period. Restrictive disease secondary to fibrosis is typically seen with more chronic disease. Diffusion capacity of carbon monoxide measurements are typically elevated in the setting of pulmonary hemorrhage because of the strong affinity of the intra-alveolar hemoglobin for carbon monoxide.

TREATMENT
In the setting of massive blood loss, volume resuscitation and transfusion of blood products are necessary. Maintenance of adequate ventilation and circulatory function is crucial. Rigid bronchoscopy may be utilized for localization of bleeding and for removal of debris but active bleeding may be exacerbated by airway manipulation. Flexible bronchoscopy and bronchoalveolar lavage may be required for diagnosis. Ideally, treatment is directed at the specific pathologic process responsible for the hemorrhage. When bronchiectasis is a known entity and a damaged artery can be localized, bronchial artery embolization is often the therapy of choice. If embolization fails, total or partial lobectomy may be required. Embolization is the initial treatment of choice for an arteriovenous malformation. In circumstances of diffuse hemorrhage, corticosteroids and other immunosuppressive agents have been shown to be of benefit. Prognosis depends largely on the underlying disease process and the chronicity of bleeding.

Bibliography is available at Expert Consult.
Bibliography
Atelectasis is the incomplete expansion or complete collapse of air-bearing tissue, resulting from obstruction of air intake into the alveolar sacs. Segmental, lobar, or whole lung collapse is associated with the absorption of air contained in the alveoli, which are no longer ventilated.

**PATHOPHYSIOLOGY**

The causes of atelectasis can be divided into 5 groups (Table 408-1). Respiratory syncytial virus (see Chapter 260) and other viral infections, including influenza viruses in young children can cause multiple areas of atelectasis. Mucous plugs are a common predisposing factor to atelectasis. Massive collapse of 1 or both lungs is most often a post-operative complication but occasionally results from other causes, such as trauma, asthma, pneumonia, tension pneumothorax (see Chapter 411), aspiration of foreign material (see Chapters 387 and 397), and paralysis, or after extubation. Massive atelectasis is usually produced by a combination of factors, including immobilization or decreased use of the diaphragm and the respiratory muscles, obstruction of the bronchial tree, and abolition of the cough reflex.

**CLINICAL MANIFESTATIONS**

Symptoms vary with the cause and extent of the atelectasis. A small area is likely to be asymptomatic. When a large area of previously normal lung becomes atelectatic, especially when it does so suddenly, dyspnea accompanied by rapid shallow respirations, tachycardia, cough, and often cyanosis occurs. If the obstruction is removed, the symptoms disappear rapidly. Although it was once believed that atelectasis alone can cause fever, studies have shown no association between atelectasis and fever. Physical findings include limitation of chest excursion, decreased breath sound intensity, and coarse crackles. Breath sounds are decreased or absent over extensive atelectatic areas.

<table>
<thead>
<tr>
<th>Table 408-1 Anatomic Causes of Atelectasis</th>
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<tbody>
<tr>
<td><strong>CAUSE</strong></td>
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<tr>
<td>External compression on the pulmonary parenchyma</td>
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<tr>
<td>Endobronchial obstruction completely obstructing the ingress of air</td>
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<tr>
<td>Intraluminal obstruction of a bronchus</td>
</tr>
<tr>
<td>Intrabronchiolar obstruction</td>
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<tr>
<td>Respiratory compromise or paralysis</td>
</tr>
</tbody>
</table>

**DIAGNOSIS**

The diagnosis of atelectasis can usually be established by chest radiographic examination. Typical findings include volume loss and displacement of fissures. Atypical presentations include atelectasis manifesting as a mass like opacity and atelectasis in an unusual location. Lobar atelectasis may be associated with pneumothorax.

In asthmatic children, chest radiography demonstrates an abnormality rate of 44%, compared with a thorax high-resolution CT scan abnormality rate of 75%. Children with asthma and atelectasis have an increased incidence of right middle lobe syndrome, acute asthma exacerbations, pneumonia, and upper airway infections.

In foreign-body aspiration, atelectasis is one of the most common radiographic findings. The site of atelectasis usually indicates the site of the foreign body (see Chapter 377.1). Atelectasis is more common when diagnosis of foreign-body aspiration is delayed for greater than 2 wk.

Bronchoscopic examination reveals a collapsed main bronchus when the obstruction is at the tracheobronchial junction and may also disclose the nature of the obstruction.

Massive pulmonary atelectasis is generally diagnosed on chest radiograph. Typical findings include elevation of the diaphragm, narrowing of the intercostal spaces, and displacement of the mediastinal structures and heart toward the affected side (Fig. 408-1).

**TREATMENT**

Treatment depends on the cause of the collapse. If effusion or pneumothorax is responsible, the external compression must first be removed. Often vigorous efforts at cough, deep breathing, and percussion will facilitate expansion. Aspiration with sterile tracheal catheters may facilitate removal of mucous plugs. Continuous positive airway pressure may improve atelectasis.

Bronchoscopic examination is immediately indicated if atelectasis is the result of a foreign body or any other bronchial obstruction that can be relieved. For bilateral atelectasis, bronchoscopic aspiration should also be performed immediately. It is also indicated when an isolated area of atelectasis persists for several weeks. If no anatomic basis for atelectasis is found and no material can be obtained by suctioning, the introduction of a small amount of saline followed by suctioning allows recovery of bronchial secretions for culture and, possibly, for cytologic examination. Frequent changes in the child’s position, deep breathing, and chest physiotherapy may be beneficial. Intrapulmonary percussive ventilation is a chest physiotherapy technique that is safe and effective. Oxygen therapy is indicated when there is dyspnea or desaturation. Intermittent positive-pressure breathing and incentive spirometry are recommended when atelectasis does not improve after chest physiotherapy.

In some conditions, such as asthma, bronchodilator and corticosteroid treatment may accelerate atelectasis clearance. Recombinant
human deoxyribonuclease, which is approved only for the treatment of cystic fibrosis, has been used off-label for patients without cystic fibrosis who have persistent atelectasis. This product reduces the viscosity of purulent bronchial debris. In patients with acute severe asthma, diffuse airway plugging with thick viscous secretions frequently occurs, with the resulting atelectasis often refractory to conventional therapy. Recombinant human deoxyribonuclease is used in both nebulized form for nonintubated patients with acute asthma as well as intratracheally for atelectasis in intubated asthmatics, with resolution of atelectasis unresponsive to conventional asthma therapies. Recombinant human deoxyribonuclease is also utilized in ventilated infants and children with atelectasis not caused by asthma.

Hypertonic saline solution increases mucociliary clearance in patients with asthma, bronchiectasis, and cystic fibrosis and infants with acute bronchiolitis. It is delivered via nebulization either via face mask or endotracheal tube. It can be delivered alone or in combination with a bronchodilator. This therapy is being utilized in the outpatient and inpatient setting, as well as in both the neonatal intensive care unit and the pediatric intensive care unit, to help facilitate airway clearance.

Lobar atelectasis in cystic fibrosis is discussed in Chapter 403. Atelectasis can occur in patients with neuromuscular diseases. These patients tend to have ineffective cough and difficulty expelling respiratory tract secretions, which lead to pneumonia and atelectasis. Several devices and treatments are available to assist these patients, including intermittent positive-pressure breathing, a mechanical insufflator-exsufflator, and noninvasive bilevel positive-pressure ventilation via nasal mask or full-face mask. Patients with neuromuscular disease who have undergone surgery are at substantial risk for postoperative atelectasis and subsequent pneumonia. Migrating atelectasis in the newborn infant, a rare and unique presentation, may be secondary to neuromuscular disease.

There is an association between the development of lobar collapse and the requirement for mechanical ventilation. Although lobar collapse is rarely a cause of long-term morbidity, its occurrence may necessitate the prolongation of mechanical ventilation or re-intubation.

### Table 408-2

<table>
<thead>
<tr>
<th>Benefit of Airway Clearance Therapies in Pediatric Conditions</th>
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<tbody>
<tr>
<td>CLEAR AND PROVEN BENEFIT</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>PROBABLE BENEFIT</td>
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<tr>
<td>Neuromuscular disease</td>
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<tr>
<td>Cerebral palsy</td>
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<tr>
<td>Atelectasis in children undergoing mechanical ventilation</td>
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<td>POSSIBLE BENEFIT</td>
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<td>Prevention of postextubation atelectasis in neonates</td>
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<tr>
<td>MINIMAL TO NO BENEFIT</td>
</tr>
<tr>
<td>Acute asthma</td>
</tr>
<tr>
<td>Bronchiolitis</td>
</tr>
<tr>
<td>Hyaline membrane disease</td>
</tr>
<tr>
<td>Respiratory failure without atelectasis</td>
</tr>
<tr>
<td>Prevention of atelectasis immediately following surgery</td>
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</table>


In ventilated patients, positive end-expiratory pressure or continuous positive airway pressure is generally indicated.

Airway clearance therapies utilized for adults are often recommended and/or utilized in pediatric populations. However, given the differences in respiratory physiology and anatomy between children and adults, practices applicable to one may or may not apply to the other. Atelectasis caused by cystic fibrosis is the only pediatric entity that clearly benefits from airway clearance therapy, although atelectasis caused by neuromuscular disease, cerebral palsy, or mechanical ventilation probably benefits from such therapy (Table 408-2). Thus far no specific airway clearance therapy has been demonstrated to be superior.

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


ETIOLOGY
Primary tumors of the lung are rare in children and adolescents. An accurate estimate of frequency is currently not possible because the literature is composed of case reports and case series. A high incidence of “inflammatory pseudotumors” further clouds the statistics. Bronchial adenomas (including bronchial carcinoid, adenoid cystic carcinoma and mucoepidermoid carcinomas) are the most common primary tumors; bronchial carcinoid tumors represent ≈80%. Carcinoids are low-grade malignancies; carcinoid syndrome is rare in children. Metastatic lesions are the most common forms of pulmonary malignancy in children; primary processes include Wilms tumor, osteogenic sarcoma, and hepatoblastoma (see Part XXII: Cancer and Benign Tumors). Adenocarcinoma and undifferentiated histology are the most common pathologic findings in primary lung cancer; pulmonary blastoma is rarer and frequently occurs in the setting of cystic lung disease. Mediastinal involvement with lymphoma is more common than primary pulmonary malignancies.

CLINICAL MANIFESTATIONS AND EVALUATION
Pulmonary tumors may manifest as fever, hemoptysis, wheezing, cough, pleural effusion, chest pain, dyspnea, or recurrent or persistent pneumonia or atelectasis. Localized wheezing, and wheezing unresponsive to bronchodilators, can occur with bronchial tumors. Tumors may be suspected from plain chest radiographs; CT scanning of the chest is necessary for precise anatomic definition (Fig. 409-1). Depending on the tumor size and location, pulmonary function tests may be normal or show an obstructive, restrictive, or mixed pattern; as with the physical exam, there is no responsiveness to bronchodilators. Bronchial tumors are occasionally diagnosed during fiberoptic bronchoscopy performed for persistent or recurrent pulmonary infiltrates or for hemoptysis.

Patients with symptoms or with radiographic or other laboratory findings suggesting pulmonary malignancy should be evaluated carefully for a tumor at another site before surgical excision is carried out. Isolated primary lesions and isolated metastatic lesions discovered long after the primary tumor has been removed are best treated by excision. The prognosis varies and depends on the type of tumor involved; outcomes for inflammatory pseudotumors and primary pulmonary carcinoid tumors treated with resection are good.

Bibliography is available at Expert Consult.

Figure 409-1 Endobronchial mucoepidermoid carcinoma in a 10 yr old boy who presented with cough and fever. A, The chest radiograph shows a left upper lobe mass, a hyperinflated left lower lobe, and a prominent left hilum. B, The CT scan shows complete obstruction of the left upper lobe bronchus by a low-attenuation mass that extends into the left mainstem bronchus. (From Slovis TL, editor: Caffey’s pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 78-20.)
Bibliography


Chapter 410

Pleurisy, Pleural Effusions, and Empyema

Glenna B. Winnie and Steven V. Lossef

Pleurisy is the inflammation of the pleura; it may be accompanied by an effusion. The most common cause of pleural effusion in children is bacterial pneumonia (see Chapter 400); heart failure (see Chapter 442), rheumatologic causes, and metastatic intrathoracic malignancy are the next most common causes. A variety of other diseases account for the remaining cases, including tuberculosis (see Chapter 215), lupus erythematosus (see Chapter 158), aspiration pneumonitis (see Chapter 397), uremia, pancreatitis, subdiaphragmatic abscess, and rheumatoid arthritis. Males and females are affected equally.

Inflammatory processes in the pleura are usually divided into 3 types: dry or plastic, serofibrinous or serosanguineous, and purulent pleurisy or empyema.

410.1 Dry or Plastic Pleurisy (Pleural Effusion)

Glenna B. Winnie and Steven V. Lossef

ETIOLOGY
Plastic pleurisy may be associated with acute bacterial or viral pulmonary infections or may develop during the course of an acute upper respiratory tract illness. The condition is also associated with tuberculosis and connective tissue diseases such as rheumatic fever.
PATHOLOGY AND PATHOGENESIS
The process is usually limited to the visceral pleura, with small amounts of yellow serous fluid and adhesions between the pleural surfaces. In tuberculosis, the adhesions develop rapidly and the pleura are often thickened. Occasionally, fibrin deposition and adhesions are severe enough to produce a fibrothorax that markedly inhibits the excursions of the lung.

CLINICAL MANIFESTATIONS
The primary disease often overshadows signs and symptoms. Pain, the principal symptom, is exaggerated by deep breathing, coughing, and straining. Occasionally, pleural pain is described as a dull ache, which is less likely to vary with breathing. The pain is often localized over the chest wall and is referred to the shoulder or the back. Pain with breathing is responsible for grunting and guarding of respirations, and the child often lies on the affected side in an attempt to decrease respiratory excursions. Early in the illness, a leathery, rough, inspiratory and expiratory friction rub may be audible, but it usually disappears rapidly. If the layer of exudate is thick, increased dullness to percussion and decreased breath sounds may be heard. Pleurisy may be asymptomatic. Chronic pleurisy is occasionally encountered with conditions such as atelectasis, pulmonary abscess, connective tissue diseases, and tuberculosis.

LABORATORY FINDINGS
Plastic pleurisy may be detected on radiographs as a diffuse haziness at the pleural surface or a dense, sharply demarcated shadow (Figs. 410-1 and 410-2). The latter finding may be indistinguishable from small amounts of pleural exudate. Chest radiographic findings may be normal, but ultrasonography or CT findings will be positive.

Figure 410-1 A, Right pleural effusion (asterisk) caused by lupus erythematosus in a 12 yr old child. Note compressed middle and lower lobes of the right lung (arrows). B, The effusion was evacuated and the right lung was completely reexpanded after insertion of the pigtail chest tube (arrow).

Figure 410-2 Left pleural effusion in a teenager with AIDS and Mycobacterium avium-intracellulare infection. The pleural effusion (asterisk) is clearly seen on the chest radiograph (A), CT scan (B), and ultrasonogram (C) of the left chest. Arrows point to the compressed and atelectatic left lung. D, A pigtail chest tube (arrowhead) was inserted, resulting in reexpansion of the left lung.
Bibliography

DIFFERENTIAL DIAGNOSIS
Plastic pleurisy must be distinguished from other diseases, such as epidemic pleurodynia, trauma to the rib cage (rib fracture), lesions of the dorsal root ganglia, tumors of the spinal cord, herpes zoster, gall-bladder disease, and trichinosis. Even if evidence of pleural fluid is not found on physical or radiographic examination, a CT- or ultrasound-guided pleural tap in suspected cases often results in the recovery of a small amount of exudate, which when cultured may reveal the underlying bacterial cause in patients with an acute pneumonia. Patients with pleurisy and pneumonia should always be screened for tuberculosis.

TREATMENT
Therapy should be aimed at the underlying disease. When pneumonia is present, neither immobilization of the chest with adhesive plaster nor therapy with drugs capable of suppressing the cough reflex is indicated. If pneumonia is not present or is under good therapeutic control, strapping of the chest to restrict expansion may afford relief from pain. Analgesia with nonsteroidal antiinflammatory agents may be helpful.

Bibliography is available at Expert Consult.

410.2 Serofibrinous or Serosanguineous Pleurisy (Pleural Effusion)
Glenna B. Winnie

ETIOLOGY
Serofibrinous pleurisy is defined by a fibrinous exudate on the pleural surface and an exudative effusion of serous fluid into the pleural cavity. Generally it is associated with infections of the lung or with inflammatory conditions of the abdomen or mediastinum; occasionally, it is found with connective tissue diseases such as lupus erythematosus, periarteritis, and rheumatoid arthritis, and it may be seen with primary or metastatic neoplasms of the lung, pleura, or mediastinum; tumors are commonly associated with a hemorrhagic pleurisy.

PATHOGENESIS
Pleural fluid originates from the capillaries of the parietal pleura and is absorbed from the pleural space via pleural stomata and the lymphatics of the parietal pleura. The rate of fluid formation is dictated by the Starling law, by which fluid movement is determined by the balance of hydrostatic and osmotic pressures in the pleural space and pulmonary capillary bed, and the permeability of the pleural membrane. Normally, only 4-12 mL of fluid is present in the pleural space, but if formation exceeds clearance, fluid accumulates. Pleural inflammation increases the permeability of the pleural surface, with increased proteinaceous fluid formation; there may also be some obstruction to lymphatic absorption.

CLINICAL MANIFESTATIONS
Because serofibrinous pleurisy is often preceded by the plastic type, early signs and symptoms may be those of plastic pleurisy. As fluid accumulates, pleuritic pain may disappear. The patient may become asymptomatic if the effusion remains small, or there may be only signs and symptoms of the underlying disease. Large fluid collections can produce cough, dyspnea, retraction, tachypnea, orthopnea, or cyanosis.

Physical findings depend on the amount of effusion. Dullness to flattness may be found on percussion. Breath sounds are decreased or absent, and there is a diminution in tactile fremitus, a shift of the mediastinum away from the affected side, and, occasionally, fullness of the intercostal spaces. If the fluid is not loculated, these signs may shift with changes in position. If extensive pneumonia is present, crackles and rhonchi may also be audible. Friction rubs are usually detected only during the early or late plastic stage. In infants, physical signs are less definite, and bronchial breathing may be heard instead of decreased breath sounds.

LABORATORY FINDINGS
Radiographic examination shows a generally homogeneous density obliterating the normal markings of the underlying lung. Small effusions may cause obliteration of only the costophrenic or cardiophrenic angles or a widening of the interlobar septa. Examinations should be performed with the patient both supine and upright, to demonstrate a shift of the effusion with a change in position; the decubitus position may be helpful. Ultrasonographic examinations are useful and may guide thoracentesis if the effusion is loculated. Examinations of the fluid is essential to differentiate exudates from transudates and to determine the type of exudate. Depending on the clinical scenario, pleural fluid is sent for culture for bacterial, fungal, and mycobacterial cultures; antigen testing; Gram staining; and chemical evaluation of content, including protein, lactate dehydrogenase and glucose, amylase, specific gravity, total cell count and differential, cytologic examination, and pH. Complete blood count and serum chemistry analysis should be obtained; hypoalbuminemia is often present. Exudates usually have at least 1 of the following features: protein level >3.0 g/dL, with pleural fluid : serum protein ratio >0.5; pleural fluid lactate dehydrogenase values >200 IU/L; or fluid : serum lactate dehydrogenase ratio >0.6.

Although systemic acidosis reduces the usefulness of pleural fluid pH measurements, pH <7.20 suggests an exudate (see Chapter 400). Glucose is usually <60 mg/dL in malignancy, rheumatoid disease, and tuberculosis; the finding of many small lymphocytes and a pH <7.20 suggest tuberculosis. The fluid of serofibrinous pleurisy is clear or slightly cloudy and contains relatively few leukocytes and, occasionally, some erythrocytes. Gram staining may occasionally show bacteria; however, acid-fast staining rarely demonstrates tubercle bacilli.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS
Thoracentesis should be performed when pleural fluid is present or is suggested, unless the effusion is small and the patient has a classic-appearing lobar pneumococcal pneumonia. Thoracentesis can differentiate serofibrinous pleurisy, empyema, hydrothorax, hemotherax, and chylothorax. Exudates are usually associated with an infectious process. In hydrothorax, the fluid has a specific gravity <1.015, and evaluation reveals only a few mesothelial cells rather than leukocytes. Chylothorax and hemotherax usually have fluid with a distinctive appearance, but differentiating serofibrinous from purulent pleurisy is impossible without microscopic examination of the fluid. Cytologic examination may reveal malignant cells. Serofibrinous fluid may rapidly become purulent.

COMPLICATIONS
Unless the fluid becomes purulent, it usually disappears relatively rapidly, particularly with appropriate treatment of bacterial pneumonia. It persists somewhat longer if a result of tuberculosis or a connective tissue disease and may recur or remain for a long time if caused by a neoplasm. As the effusion is absorbed, adhesions often develop between the 2 layers of the pleura, but usually little or no functional impairment results. Pleural thickening may develop and is occasionally mistaken for small quantities of fluid or for persistent pulmonary infiltrates. Pleural thickening may persist for months, but the process usually disappears, leaving no residua.

TREATMENT
Therapy should address the underlying disease. With a large effusion, draining the fluid makes the patient more comfortable. When a diagnostic thoracentesis is performed, as much fluid as possible should be removed for therapeutic purposes. Rapid removal of ≥1 L of pleural fluid may be associated with the development of reexpansion pulmonary edema (see Chapter 396). If the underlying disease is adequately treated, further drainage is usually unnecessary, but if sufficient fluid reaccumulates to cause respiratory embarrassment, chest tube drainage should be performed. In older children with suspected parapneumonic effusion, tube thoracostomy is considered necessary if the pleural fluid pH is <7.20 or the pleural fluid glucose level is <50 mg/dL. If the fluid is clearly purulent, tube drainage with thrombolytic therapy or less often video-assisted thoracoscopic surgery (VATS) is indicated.

Bibliography is available at Expert Consult.
Bibliography


Patients with pleural effusions may need analgesia, particularly after thoracentesis or insertion of a chest tube. Those with acute pneumonia may need supplemental oxygen in addition to specific antibiotic treatment.

Bibliography is available at Expert Consult.

410.3 Purulent Pleurisy or Empyema
Glenna B. Winnie and Steven V. Lossef

ETIOLOGY
Empyema is an accumulation of pus in the pleural space. It is most often associated with pneumonia (see Chapter 400) caused by Streptococcus pneumoniae (see Chapter 182), although Staphylococcus aureus (see Chapter 181.1) is most common in developing nations and Asia, as well as in posttraumatic empyema. The relative incidence of Haemophilus influenzae (see Chapter 194) empyema has decreased since the introduction of the H. influenzae type b vaccination. Group A streptococcus, Gram-negative organisms, tuberculosis, fungi, and malignancy are less common causes. The disease can also be produced by rupture of a lung abscess into the pleural space, by contamination introduced from trauma or thoracic surgery, or, rarely, by mediastinitis or the extension of intraabdominal abscesses.

EPIDEMIOLOGY
Empyema is most frequently encountered in infants and preschool children. It is increasing in frequency. It occurs in 5-10% of children with bacterial pneumonia and in up to 86% of children with necrotizing pneumonia.

PATHOLOGY
Empyema has 3 stages: exudative, fibrinopurulent, and organizational. During the exudative stage, fibrinous exudate forms on the pleural surfaces. In the fibrinopurulent stage, fibrinous septa form, causing loculation of the fluid and thickening of the parietal pleura. If the pus is not drained, it may dissect through the pleura into lung parenchyma, producing bronchopleural fistulas and pyopneumothorax, or into the abdominal cavity. Rarely, the pus dissects through the chest wall (i.e., empyema necessitatis). During the organizational stage, there is fibroblast proliferation; pockets of loculated pus may develop into thick-walled abscess cavities or the lung may collapse and become surrounded by a thick, inelastic envelope (peel).

CLINICAL MANIFESTATIONS
The initial signs and symptoms are primarily those of bacterial pneumonia. Children treated with antibiotic agents may have an interval of a few days between the clinical pneumonia phase and the evidence of empyema. Most patients are febrile, develop increased work of breathing or respiratory distress, and often appear more ill. Physical findings are identical to those described for serofibrinous pleurisy, and the 2 conditions are differentiated only by thoracentesis, which should always be performed when empyema is suspected.

LABORATORY FINDINGS
Radiographically, all pleural effusions appear similar, but the absence of a shift of the fluid with a change of position indicates a loculated empyema (Figs. 410-3 to 410-5). Septa may be confirmed by ultrasonography or CT. The maximal amount of fluid obtainable should be withdrawn by thoracentesis and studied as described in Chapter 410.2. The effusion is empyema if bacteria are present on Gram staining, the pH is <7.20, and there are >100,000 neutrophils/µL (see Chapter 400). The appearance of pus produced by different organisms is not distinctive; cultures of the fluid must always be performed. In pneumococcal empyema, the culture is positive in 58% of cases. In patients with negative culture results for pneumococcus, the pneumococcal polymerase chain reaction analysis is most helpful to making a diagnosis. Blood cultures may be positive and have a higher yield than cultures of the pleural fluid. Leukocytosis and an elevated sedimentation rate may be found.

COMPLICATIONS
With staphylococcal infections, bronchopleural fistulas and pyopneumothorax commonly develop. Other local complications include purulent pericarditis, pulmonary abscesses, peritonitis from extension through the diaphragm, and osteomyelitis of the ribs. Septic complications such as meningitis, arthritis, and osteomyelitis may also occur. Septicemia is often encountered in H. influenzae and pneumococcal infections. The effusion may organize into a thick “peel,” which may restrict lung expansion and may be associated with persistent fever and temporary scoliosis.

TREATMENT
The aim of empyema treatment is to sterilize pleural fluid and restore normal lung function. Treatment includes systemic antibiotics and thoracentesis and chest tube drainage initially with a fibrinolytic agent; if no improvement occurs, VATS is indicated. Open decortication is indicated if fibrinolysis and VATS are ineffective (see Chapter 411). If empyema is diagnosed early, antibiotic treatment plus thoracentesis achieves a complete cure. The selection of antibiotic should be based on the in vitro sensitivities of the responsible organism. See Chapters 181, 182, and 194 for treatment of infections by Staphylococcus, S. pneumoniae, and H. influenzae, respectively. Clinical response in empyema is slow; even with optimal treatment, there may be little improvement for as long as 2 wk. With staphylococcal infections, resolution is very slow, and systemic antibiotic therapy is required for 3-4 wk. Instillation of antibiotics into the pleural cavity does not improve results.
When pus is obtained by thoracentesis, closed-chest tube drainage with fibrinolysis is the initial procedure followed by VATS if there is no improvement. Multiple aspirations of the pleural cavity should not be attempted. If pleural fluid septa are detected on ultrasound, fibrinolysis is attempted followed by VATS if no improvement is noted. Closed-chest tube drainage is controlled by an underwater seal or continuous suction; sometimes more than 1 tube is required to drain loculated areas. Closed drainage is usually continued for 5-7 days. Chest tubes that are no longer draining are removed.

Instillation of fibrinolytic agents into the pleural cavity via the chest tube may promote drainage, decrease fever, lessen need for surgical intervention, and shorten hospitalization; it does not shorten the course of disease when used after VATS. The optimal drug and dosage have not been determined. Streptokinase 15,000 units/kg in 50 mL of 0.9% saline daily for 3-5 days and urokinase 40,000 units in 40 mL saline every 12 hr for 6 doses have been evaluated in randomized trials in children. Alteplase (tissue plasminogen activator) has also been used. There is a risk of anaphylaxis with streptokinase, and all 3 drugs can be associated with hemorrhage and other complications.

Extensive fibrinous changes may take place over the surface of the lungs owing to empyema, but they eventually resolve. In the child who remains febrile and dyspneic for more than 72 hr after initiation of therapy with intravenous antibiotics and thoracostomy tube drainage, surgical decortication via VATS or, less often, open thoracotomy may speed recovery. If pneumatoceles form, no attempt should be made to treat them surgically or by aspiration, unless they reach sufficient size to cause respiratory embarrassment or become secondarily infected. Pneumatoceles usually resolve spontaneously with time. The long-term clinical prognosis for adequately treated empyema is excellent, and follow-up pulmonary function studies suggest that residual restrictive disease is uncommon, with or without surgical intervention.

*Bibliography is available at Expert Consult.*

**Figure 410-4** Pneumonia and parapneumonic effusion in a 4 yr old child. **A,** Chest radiograph shows complete opacification of the right thorax as a result of a large pleural effusion. Note the shift of the mediastinum and trachea (arrow) to the left. **B,** Thoracic CT scan shows a large right pleural effusion (asterisk) surrounding and compressing the consolidated right lung (arrowhead). Note the shift of the mediastinum and tracheal carina (arrow) to the left.

**Figure 410-5** Loculated hydropneumothorax. Frontal (A) and lateral (B) chest radiographs show loculated hydropneumothorax that complicated pneumonia in a 14 yr old child. Arrows point to the horizontal air-fluid level at the interface between the intrapleural effusion and air. **C,** Thoracic CT scan helps to localize the loculated hydropneumothorax, with its air-fluid level (arrows).
Bibliography
Pneumothorax is the accumulation of extrapulmonary air within the chest, most commonly from leakage of air from within the lung. Air leaks can be primary or secondary and can be spontaneous, traumatic, iatrogenic, or catamenial (Table 411-1). Pneumothorax in the neonatal period is also discussed in Chapter 101.12.

**ETIOLOGY AND EPIDEMIOLOGY**

A primary spontaneous pneumothorax occurs without trauma or underlying lung disease. Spontaneous pneumothorax with or without...
exertion occurs occasionally in teenagers and young adults, most frequently in males who are tall, thin, and thought to have subpleural blebs. Familial cases of spontaneous pneumothorax occur and have been associated with mutations in the folliculin gene (FCLN). FCLN mutations may be seen in the Birt-Hogg-Dube syndrome (skin fibrofolliculomas, multiple basal lung cysts, renal malignancies) or in patients with familial or recurrent spontaneous pneumothoraces. Patients with collagen synthesis defects, such as Ehlers-Danlos disease (see Chapter 469) and Marfan syndrome (see Chapter 702) are unusually prone to the development of pneumothorax.

A pneumothorax arising as a complication of an underlying lung disorder but without trauma is a secondary spontaneous pneumothorax. Pneumothorax can occur in pneumonia, usually with empyema; it can also be secondary to pulmonary abscess, gangrene, infarct, rupture of a cyst or an emphysematous bleb (in asthma), or foreign bodies in the lung. In infants with staphylococcal pneumonia, the incidence of pneumothorax is relatively high. It is found in ~5% of hospitalized asthmatic children and usually resolves without treatment. Pneumothorax is a serious complication in cystic fibrosis (see Chapter 403). Pneumothorax also occurs in patients with lymphoma or other malignancies, and in graft-versus-host disease with bronchiolitis obliterans.

External chest or abdominal blunt or penetrating trauma can tear a bronchus or abdominal viscus, with leakage of air into the pleural space. Ecstasy (methylene-dioxy-methamphetamine), crack cocaine, and marijuana abuse are associated with pneumothorax.

Iatrogenic pneumothorax can complicate transthoracic needle aspiration, tracheotomy, subclavian line placement, thoracentesis, or transbronchial biopsy. It may occur during mechanical or noninvasive ventilation, high-flow nasal cannula therapy, acupuncture, and other diagnostic or therapeutic procedures.

Catamenial pneumothorax, an unusual condition that is related to menses, is associated with diaphragmatic defects and pleural blebs.

Pneumothorax can be associated with a serous effusion (hydropneumothorax), a purulent effusion (pyopneumothorax), or blood (hemothorax). Bilateral pneumothorax is rare after the neonatal period but has been reported after lung transplantation and with Mycoplasma pneumoniae infection and tuberculosis.

**PATHOGENESIS**

The tendency of the lung to collapse, or elastic recoil, is balanced in the normal resting state by the inherent tendency of the chest wall to expand outward, creating negative pressure in the intrapleural space. When air enters the pleural space, the lung collapses. Hypoxemia occurs because of alveolar hypoventilation, ventilation-perfusion mismatch, and intrapulmonary shunt. In simple pneumothorax, intrapleural pressure is atmospheric, and the lung collapses up to 30%. In complicated, or tension, pneumothorax, continuing leak causes increasing positive pressure in the pleural space, with further compression of the lung, shift of mediastinal structures toward the contralateral side, and decreases in venous return and cardiac output.

**CLINICAL MANIFESTATIONS**

The onset of pneumothorax is usually abrupt, and the severity of symptoms depends on the extent of the lung collapse and on the amount of preexisting lung disease. Pneumothorax may cause dyspnea, pain, and cyanosis. When it occurs in infancy, symptoms and physical signs may be difficult to recognize. Moderate pneumothorax may cause little displacement of the intrathoracic organs and few or no symptoms. The severity of pain usually does not directly reflect the extent of the collapse.

Usually, there is respiratory distress, with retraction, markedly decreased breath sounds, and a tympanic percussion note over the involved hemithorax. The larynx, trachea, and heart may be shifted toward the unaffected side. When fluid is present, there is usually a sharply limited area of tympany above a level of flatness to percussion. The presence of amphoric breathing or, when fluid is present in the pleural cavity, of gurgling sounds synchronous with respirations suggests an open fistula connecting with air-containing tissues.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

The diagnosis of pneumothorax is usually established by radiographic examination (Figs. 411-1 to 411-6). The amount of air outside the lung varies with time. A radiograph that is taken early shows less lung collapse than one taken later if the leak continues. Expiratory views accentuate the contrast between lung markings and the clear area of the pneumothorax (see Fig. 411-1). When the possibility of diaphragmatic hernia is being considered, a small amount of barium may be necessary to demonstrate that it is not free air but is a portion of the gastrointestinal tract that is in the thoracic cavity. Ultrasound can also be used to establish the diagnosis.

It may be difficult to determine whether a pneumothorax is under tension. Evidence of tension includes shift of mediastinal structures away from the side of the air leak. A shift may be absent in situations in which the other hemithorax resists the shift, such as in the case of bilateral pneumothorax. When the lungs are both stiff, such as in cystic fibrosis or respiratory distress syndrome, the unaffected lung may not collapse easily and shift may not occur (see Fig. 411-3). On occasion, the diagnosis of tension pneumothorax is made only on the basis of evidence of circulatory compromise or on hearing a “hiss” of rapid exit of air under tension with the insertion of the thoracostomy tube.

Pneumothorax must be differentiated from localized or generalized emphysema, an extensive emphysematous bleb, large pulmonary cysts or other cystic formations, diaphragmatic hernia, compensatory overexpansion with contralateral atelectasis, and gaseous distention of

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**Table 411-1** Causes of Pneumothorax in Children

<table>
<thead>
<tr>
<th>Classification</th>
<th>Causes</th>
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<tbody>
<tr>
<td><strong>SPONTANEOUS</strong></td>
<td>Primary idiopathic—usually resulting from ruptured subpleural blebs</td>
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<td></td>
<td>Secondary blebs</td>
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<td></td>
<td>Congenital lung disease:</td>
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<td></td>
<td>Congenital cystic adenomatoid malformation</td>
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<td></td>
<td>Bronchogenic cysts</td>
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<td></td>
<td>Pulmonary hypoplasia*</td>
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<td></td>
<td>Birt-Hogg-Dube syndrome</td>
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<td>Conditions associated with increased intrathoracic pressure:</td>
<td>Asthma</td>
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<td></td>
<td>Bronchiolitis</td>
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<td></td>
<td>Air-block syndrome in neonates</td>
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<td></td>
<td>Cystic fibrosis</td>
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<td>Airway foreign body</td>
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<td>Smoking (cigarettes, marijuana, crack cocaine)</td>
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<td>Infection:</td>
<td>Pneumatocele</td>
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<td>Lung abscess</td>
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<td>Echinococcosis</td>
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<td>Bronchopleural fistula</td>
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<td>Diffuse lung disease:</td>
<td>Langerhans cell histiocytosis</td>
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<td></td>
<td>Tuberculous</td>
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<td>Marfan syndrome</td>
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<td></td>
<td>Ehlers-Danlos syndrome</td>
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<td></td>
<td>Metastatic neoplasm—usually osteosarcoma (rare)</td>
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<td></td>
<td>Pulmonary blastoma</td>
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<tr>
<td><strong>TRAUMATIC</strong></td>
<td>Noniatrogenic</td>
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<tr>
<td></td>
<td>Penetrating trauma</td>
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<td></td>
<td>Blunt trauma</td>
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<td></td>
<td>High-flow therapy</td>
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<td>Loud music (air pressure)</td>
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<td>Iatrogenic</td>
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<td></td>
<td>Thoracotomy</td>
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<td></td>
<td>Thoracoscopy, thoracentesis</td>
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<td>Tracheostomy</td>
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<td></td>
<td>Tube or needle puncture</td>
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<td></td>
<td>Mechanical ventilation</td>
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*Associated with renal agenesis, diaphragmatic hernia, amniotic fluid leaks.

Figure 411-1 Utility of an expiratory film in detection of a small pneumothorax. A, Teenage boy with stab wound and subtle radiolucency in the left apical region (arrow) on inspiratory chest radiograph. The margin of the visceral pleura is very faintly visible. B, On an expiratory film, the pneumothorax (arrow) is more obvious as the right lung has deflated and become more opaque, providing better contrast with the air in the pleural space.

Figure 411-2 Right pneumothorax, with lung collapse of a compliant lung. Shift of the mediastinum to the left (arrow) indicates that this is a tension pneumothorax.

Figure 411-3 Right pneumothorax, with only limited collapse of a poorly compliant lung.

Figure 411-4 Pneumothorax, with collapse of right lung (arrows) caused by barotrauma in a 7 mo old child who was intubated for respiratory failure.

the stomach. In most cases, chest radiography or CT differentiates among these possibilities. In addition, CT may identify underlying pathology such as blebs (Fig. 411-7).

**TREATMENT**

Therapy varies with the extent of the collapse and the nature and severity of the underlying disease. A small (<5%) or even moderate-sized pneumothorax in an otherwise normal child may resolve without specific treatment, usually within 1 wk. A small pneumothorax complicating asthma may also resolve spontaneously. Administering 100% oxygen may hasten resolution, but patients with chronic hypoxemia should be monitored closely during administration of supplemental oxygen. Pleural pain deserves analgesic treatment. Needle aspiration may be required on an emergency basis for tension pneumothorax and is as effective as tube thoracostomy in the emergency room management of primary spontaneous pneumothorax. If the pneumothorax is recurrent, secondary, or under tension, or there is >5% collapse, chest tube drainage is necessary. Pneumothorax-complicating cystic fibrosis...
Part XIX  Respiratory System

Respiratory System frequently recurs, and definitive treatment may be justified with the first episode. Similarly, if pneumothorax complicating malignancy does not improve rapidly with observation, chemical pleurodesis or surgical thoracotomy is often necessary. In cases with severe air leak or bronchopleural fistula, occlusion with an endobronchial balloon has been successful.

Closed thoracotomy (simple insertion of a chest tube) and drainage of the trapped air through a catheter, the external opening of which is kept in a dependent position under water, is adequate to reexpand the lung in most patients; pigtail catheters are frequently used. When there have been previous pneumothoraces, it may be indicated to induce the formation of strong adhesions between the lung and chest wall by a sclerosing procedure to prevent recurrence. This can be carried out by the introduction of talc, doxycycline, or iodopovidone into the pleural space (chemical pleurodesis). Open thoracotomy through a limited incision, with plication of blebs, closure of fistula, stripping of the pleura (usually in the apical lung, where the surgeon has direct vision), and basilar pleural abrasion is also an effective treatment for recurring pneumothorax. Stripping and abrading the pleura leaves raw, inflamed surfaces that heal with sealing adhesions. Postoperative pain is comparable to that with chemical pleurodesis, but the chest tube can usually be removed in 24-48 hr, compared with the usual 72 hr minimum for closed thoracotomy and pleurodesis.

Video-assisted thoracoscopic surgery is a preferred therapy for blebectomy, pleural stripping, pleural brushing, and instillation of sclerosing agents, with somewhat less morbidity than occurs with traditional open thoracotomy. There is risk of recurrence after video-assisted thoracoscopic surgery in the pediatric population, although this is often not related to surgical failure, but rather associated with the formation of new bullae.

Pleural adhesions help prevent recurrent pneumothorax, but they also make subsequent thoracic surgery difficult. When lung transplantation may be a future consideration (e.g., in cystic fibrosis), a stepwise approach to treatment of pneumothorax has been proposed. This approach begins with observation and progresses through chest tube drainage and thorascopic and then open surgery, and finally to chemical or mechanical pleurodesis. At any step during this approach, the patient and family are given the option of the definitive procedure if they understand that its performance may make lung transplantation difficult or impossible. It should also be kept in mind that the longer a chest tube is in place, the greater the chance of pulmonary deterioration, particularly in a patient with cystic fibrosis, in whom strong coughing, deep breathing, and postural drainage are important. These are all difficult to accomplish with a chest tube in place.

Treatment of the underlying pulmonary disease should begin on admission and should be continued throughout the course of treatment directed at the air leak.

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Miller MP, Sagy M: Pressure characteristics of mechanical ventilation and incidence of pneumothorax before and after the implementation of protective lung strategies in the management of pediatric patients with severe ARDS, Chest 134:969–973, 2008.

Air or gas in the mediastinum is called pneumomediastinum.

**ETIOLOGY**
Typically, pneumomediastinum is caused by alveolar rupture during acute or chronic pulmonary disease. A diverse group of nonrespiratory entities can also cause it, and the lung is not always the source of the air. Lower respiratory tract infection is a common etiology for pneumomediastinum in children younger than age 7 yr, while acute asthma is the most common cause in older children and teenagers. Simultaneous pneumothorax is unusual in these patients. Pneumomediastinum has been reported after vomiting, dental extractions, adenotonsillectomy, high-flow nasal cannula therapy, normal menses, obstetric delivery, diabetes mellitus with ketoacidosis, acupuncture, anorexia nervosa, and inhalation of helium gas. It can also result from esophageal perforation (Boerhaave syndrome), penetrating chest trauma, or inhaled foreign body. Occasionally, no underlying cause is found.

**PATHOGENESIS**
After intrapulmonary alveolar rupture, air dissects through the perivascular sheaths and other soft tissue, planes toward the hilum, and enters the mediastinum.

**CLINICAL MANIFESTATIONS**
Dyspnea and transient stabbing chest pain that may radiate to the neck are the principal features of pneumomediastinum. Isolated abdominal pain, cough, and sore throat also occur. Pneumomediastinum is difficult to detect by physical examination alone. Subcutaneous emphysema, if present, is diagnostic. Cardiac dullness to percussion may be decreased, but the chests of many patients with pneumomediastinum are chronically overinflated, and it is unlikely that the clinician can be sure of this finding. A mediastinal “crunch” (Hamman sign) is occasionally heard but is easily confused with a friction rub.

**LABORATORY FINDINGS**
Chest radiography reveals mediastinal air, with a more distinct cardiac border than normal (Figs. 412-1 to 412-3). On the lateral projection, the posterior mediastinal structures are clearly defined, there may be a lucent ring around the right pulmonary artery, and retrosternal air can usually be seen (see Fig. 412-2). Vertical streaks of air in the mediastinum and subcutaneous air are often observed (see Fig. 412-1).

**COMPLICATIONS**
Pneumomediastinum is rarely a major problem in older children because the mediastinum can be depressurized by escape of air into the neck or abdomen. In the newborn, however, the rate at which air can leave the mediastinum is limited, and pneumomediastinum can lead to dangerous cardiovascular compromise or pneumothorax (see Chapters 101.12 and 411).

**TREATMENT**
Treatment is directed primarily at the underlying obstructive pulmonary disease or other precipitating condition. Analgesics are occasionally needed for chest pain. Rarely, subcutaneous emphysema can cause sufficient tracheal compression to justify tracheotomy; the tracheotomy also decompresses the mediastinum. Collar mediastinotomy and percutaneous drainage catheter placement are other treatment modalities.

Bibliography is available at Expert Consult.
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Figure 412-3 Sail sign—thymic elevation. (From Clark DA: Atlas of neonatology, ed 7, Philadelphia, 2000, WB Saunders, p. 94.)
Hydrothorax is a transudative pleural effusion; typically, it is caused by abnormal pressure gradients in the lung.

ETIOLOGY
Hydrothorax is most often associated with cardiac, renal, or hepatic disease. It can also be a manifestation of severe nutritional edema and hypoalbuminemia. Rarely, it results from vascular obstruction by neoplasms, enlarged lymph nodes, pulmonary embolism, or adhesions. It may occur from a ventriculoperitoneal shunt or peritoneal dialysis and has been reported in congenital parvovirus B19 infection.

CLINICAL MANIFESTATIONS
Hydrothorax is usually bilateral, but in cardiac disease it can be limited to the right side or greater on the right than on the left side. The physical signs are the same as those described for serofibrinous pleurisy (see Chapter 410.2), but in hydrothorax, there is more rapid shifting of the level of dullness with changes of position. It is usually associated with an accumulation of fluid in other parts of the body.

LABORATORY FINDINGS
The fluid is noninflammatory, has few cells, and has a lower specific gravity (<1.015) than that of a serofibrinous exudate. The ratio of pleural fluid to serum total protein is <0.5, the ratio of pleural fluid to serum lactic dehydrogenase is <0.6, and the pleural fluid lactic dehydrogenase value is less than 66% of the upper limit of the normal serum lactic dehydrogenase range.

TREATMENT
Therapy is directed at the underlying disorder; aspiration may be necessary when pressure symptoms are notable.

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Bibliography
Hemothorax, an accumulation of blood in the pleural cavity, is rare in children.

**ETIOLOGY**

Bleeding into the chest cavity most commonly occurs after chest trauma, either blunt or penetrating. It can be the result of iatrogenic trauma, including surgical procedures and venous line insertion. Hemothorax can also result from erosion of a blood vessel in association with inflammatory processes such as tuberculosis and empyema. It may complicate a variety of congenital anomalies including sequestration, patent ductus arteriosus, and pulmonary arteriovenous malformation (see Fig. 407-2 in Chapter 407). It is also an occasional manifestation of intrathoracic neoplasms, costal exostoses, blood dyscrasias, bleeding diatheses, or thrombolytic therapy. Rupture of an aneurysm is unlikely during childhood. Hemothorax may occur spontaneously in neonates and older children. A pleural hemorrhage associated with a pneumothorax is a hemopneumothorax; it is usually the result of a ruptured bulla with lung volume loss causing a torn pleural adhesion.

**CLINICAL MANIFESTATIONS**

In addition to the symptoms and signs of pleural effusion (see Chapter 410.2), hemothorax is associated with hemodynamic compromise related to the amount and rapidity of bleeding.

**Figure 414-1** Hemothorax (asterisk) and associated rib fractures (arrows) in a teenager involved in a motor vehicle accident. A, Chest radiograph. B, CT scan.
**DIAGNOSIS**
The diagnosis of a hemothorax is initially suspected from radiographs or CT scans but can be made only with thoracentesis (Fig. 414-1). In every case, an effort must be made to determine and treat the cause.

**TREATMENT**
Initial therapy is tube thoracostomy. Surgical intervention may be required to control active bleeding, and transfusion may be indicated. Inadequate removal of blood in extensive hemothorax may lead to substantial restrictive disease secondary to organization of fibrin; fibrinolytic therapy or a decortication procedure may then be necessary. Embolization is the treatment of choice for an arteriovenous malformation.

*Bibliography is available at Expert Consult.*
Bibliography
Chylothorax is a pleural collection of fluid formed by the escape of chyle from the thoracic duct or lymphatics into the thoracic cavity.

**ETIOLOGY**
Chylothorax in children occurs most frequently because of thoracic duct injury as a complication of cardiothoracic surgery (Fig. 415-1). Other cases are associated with chest injury (Fig. 415-2), extracorporeal membrane oxygenation, or with primary or metastatic intrathoracic malignancy (Fig. 415-3), particularly lymphoma. In newborns, rapidly increased venous pressure during delivery may lead to thoracic duct rupture. Less common causes include lymphangiomatosis; restrictive pulmonary diseases; thrombosis of the duct, superior vena cava, or subclavian vein; tuberculosis or histoplasmosis; and congenital anomalies of the lymphatic system (Fig. 415-4). Refractory chylothorax in the fetus has been associated with a missense mutation in integrin α9 gene. Chylothorax can occur in trauma and child abuse (see Chapter 40). It is important to establish the etiology, because treatment varies with the cause. In some patients, no specific cause is identified.

**CLINICAL MANIFESTATIONS**
The signs and symptoms of chylothorax are the same as those from pleural effusion of similar size. Chyle is not irritating, so pleuritic pain is uncommon. Onset is often gradual. However, after trauma to the thoracic duct chyle may accumulate in the posterior mediastinum for days and then rupture into the pleural space with sudden onset of dyspnea, hypotension, and hypoxemia. Approximately 50% of newborns with chylothorax present with respiratory distress in the 1st day of life. Chylothorax is rarely bilateral and usually occurs on the right side.

**LABORATORY FINDINGS**
Thoracentesis demonstrates a chylous effusion, a milky fluid containing fat, protein, lymphocytes, and other constituents of chyle; fluid may be yellow or bloody. In newborn infants or those who are not ingesting food, the fluid may be clear. A pseudochylous milky fluid may be
present in chronic serous effusion, in which fatty material arises from degenerative changes in the fluid and not from lymph. In chylothorax, the fluid triglyceride level is >110 mg/dL, the pleural fluid:serum triglyceride ratio is >1.0, and pleural fluid:serum cholesterol ratio is <1.0; lipoprotein analysis reveals chylomicrons. Fluid immunoglobulin levels are elevated. The cells are primarily T lymphocytes. Chest radiographs show an effusion; CT scans show normal pleural thickness and may reveal a lymphoma as the etiology of the chylothorax. A lymphangiogram can localize the site of the leak, and lymphoscintigraphy may demonstrate abnormalities of the lymphatic trunks and peripheral lymphatics.

**COMPLICATIONS**

Repeated aspirations may be required to relieve the symptoms of pressure. Chyle reaccumulates quickly, and repeated thoracentesis may cause malnutrition with significant loss of calories, protein, and electrolytes. Immunodeficiencies, including hypogammaglobulinemia and abnormal cell-mediated immune responses, have been associated with repeated and chronic thoracenteses for chylothorax. The loss of T lymphocytes is associated with increased risk of infection in neonates; otherwise, infection is uncommon, but patients should not receive live virus vaccines. Lack of resolution of chylothorax can lead to inanition, infection, and death.

**TREATMENT**

Spontaneous recovery occurs in >50% of cases of neonatal chylothorax. Initial therapy includes enteral feedings with a low-fat or medium-chain triglyceride, high-protein diet or parenteral nutrition. Thoracentesis is repeated as needed to relieve pressure symptoms; tube thoracostomy is often performed. If there is no resolution in 1-2 wk, total parenteral nutrition is instituted; if this measure is unsuccessful, a pleuroperitoneal shunt, thoracic duct ligation, or application of fibrin glue is considered. Surgery should be considered earlier in neonates with massive chylothorax and chyle output of >50 mL/kg/day despite maximum medical therapy for 3 days. Parenteral octreotide at a dose of 0.5-1 µg/kg/hr to a maximum of 10 µg/kg/day intravenously has been used to manage chylothorax, but further study is needed. Other therapeutic approaches include percutaneous thoracic duct embolization, pressure control ventilation with positive end-expiratory pressure, talc or iodopovidone pleurodesis, and inhalation of nitric oxide. Treatment is similar for traumatic chylothorax. Chemical pleurodesis or irradiation is used in malignant chylothorax. OK432 (picibanil) has been used to treat fetal and newborn chylothorax.

*Bibliography is available at Expert Consult.*
Bibliography
Bronchopulmonary dysplasia (BPD) is a pathologic process leading to signs and symptoms of chronic lung disease that originates in the neonatal period (see Chapter 101). The pathogenesis of lung disease in the population of neonates weighing <1,000 g includes the contribution of immature development of airway and vascular structures of the lung. The currently accepted definition includes an oxygen requirement for 28 days postnatally, and the disorder is graded as mild, moderate, or severe on the basis of supplemental oxygen requirement and gestational age (Table 416-1).

CLINICAL MANIFESTATIONS

Physical findings of the pulmonary exam vary with the severity of disease. Tachypnea is a common finding. Mouth breathing because of narrowed nasal passages and high arched palate is noted on upper airway exam. The chest demonstrates an increased anteroposterior diameter that suggests air trapping. Intercostal retractions are frequently present. Although breath sounds are frequently clear when the patient is well and abnormal only during an acute exacerbation, many patients have baseline wheeze or coarse crackles. A persistent fixed wheeze or stridor suggests subglottic stenosis (see Chapter 388) or large airway malacia. Fine crackles may be present in patients prone to fluid overload.

The most severely affected patients require prolonged mechanical ventilation to achieve acceptable gas exchange. Supplemental oxygen may be required to maintain acceptable oxygen saturation and often is needed to minimize the work of breathing. Infants with significant lung disease exhibit growth failure from the elevated energy expenditure essential to maintain the increased metabolic demands of respiration. Chronic respiratory insufficiency may be evident as elevation of serum bicarbonate, elevation of pressure of carbon dioxide on blood gas analysis, or polycythemia.

Patients must be monitored for the development of cor pulmonale, especially if they require supplemental oxygen and have chronic respiratory insufficiency.
Gastroesophageal reflux disease (GERD) (see Chapter 323) and pulmonary aspiration complicate pulmonary status, particularly during an exacerbation when the infant is most tachypneic and when pulmonary mechanics increase the risk of GERD. Other conditions resulting from premature birth–complicating BPD include upper airway obstruction leading to hypoxia, neurodevelopmental delay with increased risk of aspiration, systemic hypertension with left ventricular hypertrophy, poor growth, and electrolyte disturbances.

In severely affected patients and patients with disease disproportionate to their risk for development of chronic lung disease, other pulmonary disease must be suspected, such as asthma (see Chapter 144), cystic fibrosis (see Chapter 403), and chronic aspiration pneumonia (see Chapter 398). Recurrent episodes of respiratory distress are common, but anatomic airway abnormalities, such as subglottic stenosis (see Chapter 388) and airway malacia (see Chapter 386), must also be considered.

A pulmonary exacerbation of BPD is typically triggered during viral upper respiratory infections. Other frequent triggers include viral lower respiratory infections, sinusitis, otitis media, weather changes, exposure to cigarette smoke, and exacerbations of gastroesophageal reflux. During an exacerbation, the infant exhibits increased work of breathing, with tachypnea and retractions becoming more prominent. Chest wall configuration may change, with an increased anteroposterior diameter. If wheezing is a prominent baseline finding, poor air entry during an exacerbation may result in less wheezing, signifying a significant deterioration of respiratory status.

**TREATMENT**

Treatment is directed toward decreasing the work of breathing and normalizing gas exchange, to allow for optimal growth and neurodevelopment. Infants requiring supplemental oxygen past 35 wk postmenstrual age have a higher incidence of lower airway obstruction and bronchodilator responsiveness and are more likely to be hospitalized during the toddler years than their peers. The etiology of wheezing in BPD may be lower airway inflammation, bronchial smooth muscle irritation, bronchial smooth muscle hypertrophy, and airway malacia. The administration of an inhaled bronchodilator is frequently undertaken to evaluate an individual’s response. Most commonly, inhaled β-agonists initially increase air movement and improve comfort of breathing, resulting in short-term improvement in pulmonary function values. For patients whose symptoms respond, the medication should be continued, especially during high-risk periods when triggers are present, such as an upper respiratory infection or hot humid days.

β-Agonists may worsen the air exchange, particularly in infants with BPD and concomitant airway malacia. Bronchial smooth muscle may maintain airway caliber in the affected airway; smooth muscle relaxation after administration of a β-agonist results in increased small airway collapse. Patients in whom β-agonists have these effects may benefit from alternative bronchodilators, such as inhaled ipratropium and oral methylxanthines. The administration of preventive anti-inflammatory medications, such as inhaled glucocorticoids and leukotriene-modifying agents, may be considered in patients with frequent inflammatory triggers.

Targeted goals for supplemental oxygen therapy after discharge from the nursery are to improve oxygen saturation values and decrease likelihood of desaturation, reduce the risk of cor pulmonale, diminish the work of breathing, and improve growth. This therapy likely improves neurodevelopmental outcome and may decrease exacerbations caused by hypoxia. Oxygen saturation values should exceed 90%, but the optimal goal above this level is unknown. The addition of diuretic therapy with furosemide or thiazides may improve pulmonary mechanics by decreasing lung water and allow tapering of supplemental oxygen. Therapy beyond several weeks, however, is not known to improve outcome and places the child at risk for electrolyte disorders.

Adequate caloric intake can be difficult for many reasons, including oral aversion, discoordination suck and swallow, GERD, aspiration, and aspiration with GERD. In addition, tachypnea, episodic respiratory distress, increased work of breathing, and requirement for supplemental oxygen place the infant at risk for growth failure. A high caloric intake is necessary, with ranges of 120–160 kcal/kg/day required, frequently in combination with fluid restriction. To provide such high caloric intake in the compromised infant, supplemental feedings through a nasogastric or gastrostomy tube may be considered. Careful attention is necessary to maintain fluid balance.

Gastroesophageal reflux is common and must be suspected in patients not showing response to therapy and in patients with frequent exacerbations, especially exacerbations without clear triggers. Definitive diagnosis is necessary because these patients will be subject to prolonged promotility and antacid medications. Appropriate antireflux therapy in infants with GERD decreases respiratory complications. Gastroesophageal reflux with pulmonary aspiration or aspiration alone may manifest as chronic chest congestion, wheezing, and episodic hypoxic spells. Fundoplication with a gastrostomy tube is performed in patients showing no response to medical therapy. Evaluation and treatment by a speech therapist, pediatric pulmonologist, or otolaryngologist may decrease the risk for development of chronic lung disease associated with aspiration.

Prevention of respiratory viral illness is vitally important; frequent handwashing by caregivers, especially before they handle the baby and avoidance of contact with children and adults with current respiratory symptoms are essential. Respiratory syncytial virus (see Chapter 260) immunoprophylaxis should be considered on the basis of the severity of lung disease, as well as the patient’s gestational age and current age.

The prognosis for infants with BPD is generally good. Through school age, the family can expect frequent medical interactions for episodes of respiratory distress, commonly triggered by simple upper respiratory tract infections and weather changes. Pulmonary function in severely affected patients remains decreased, and exercise limitation may be present because of dyspnea. The most severely affected patients benefit from care administered by a multidisciplinary team of caregivers, including the pediatrician, pulmonologist, speech therapist, nutritionist, and developmental specialists.

Bibliography is available at Expert Consult.
Bibliography
Pulmonary function is influenced by the structure of the chest wall (see Chapter 373). Chest wall abnormalities can lead to restrictive or obstructive pulmonary disease, impaired respiratory muscle strength, and decreased ventilatory performance in response to physical stress. The congenital chest wall deformities include pectus excavatum, pectus carinatum, sternal clefs, Poland syndrome, and skeletal and cartilage dysplasias. Vertebral anomalies such as kyphoscoliosis can alter pulmonary function in children and adolescents.

### 417.1 Pectus Excavatum (Funnel Chest)

#### ETIOLOGY

Pectus excavatum, midline narrowing of the thoracic cavity is usually an isolated skeletal abnormality. The cause is unknown. Pectus excavatum can occur in isolation or it may be associated with a connective tissue disorder (Marfan [see Chapter 702] or Ehlers-Danlos syndrome [see Chapter 659]). It may be acquired secondarily to chronic lung disease, neuromuscular disease, or trauma.

#### EPIDEMIOLOGY

Pectus excavatum occurs in 1 in 400 births with a 9:1 male preponderance and accounts for >90% of congenital chest wall anomalies. There is a positive family history in one-third of cases.

#### CLINICAL MANIFESTATIONS

The deformity is present at or shortly after birth in one-third of cases but is usually not associated with any symptoms at that time. In time, fatigue, chest pain, palpitations, recurrent respiratory infections, wheezing, stridor, and cough may be present. Decreased exercise tolerance is one of the most common symptoms. Because of the cosmetic nature of this deformity, children may experience significant psychologic stress. Physical examination may reveal sternal depression, protracted shoulders, kyphoscoliosis, dorsal lordosis, inferior rib flares, rib cage rigidity, forward head tilt, scapular winging, and loss of vertebral contours (Fig. 417-1). Patients exhibit paroxysmal sternal motion and a shift of point of maximal impulse to the left. Innocent systolic murmurs may be heard.

#### LABORATORY FINDINGS

Lateral chest radiograms demonstrate the sternal depression. Use of the Haller index on chest CT (maximal internal transverse diameter of the chest divided by the minimal anteroposterior diameter at the same level) in comparison with age- and gender-appropriate normative values for determining the extent of depression of the chest wall anomaly has become useful in determining the extent of the anatomic abnormality. An electrocardiogram may show a right-axis deviation or Wolff-Parkinson-White syndrome (see Chapter 436); an echocardiogram may demonstrate mitral valve prolapse (see Chapter 428.3) and ventricular compression. Results of static pulmonary function tests may be normal but commonly show an obstructive defect in the lower airways and, less commonly, a restrictive defect as the result of abnormal chest wall mechanics. Exercise testing may demonstrate either normal tolerance or limitations from underlying cardiopulmonary dysfunction that are associated with the severity of the defect. Ventilatory limitations are commonly seen in younger children and adolescents, whereas cardiac limitations secondary to stroke volume impairments are more commonly seen in older adolescents and young adults.

#### TREATMENT

Treatment is based on the severity of the deformity and the extent of physiologic compromise as defined by physical examination and physiologic assessment of cardiopulmonary function (lung function and exercise tolerance assessment). Therapeutic options include careful observation, use of physical therapy to address musculoskeletal compromise, and corrective surgery. For patients with significant physiologic compromise, surgical correction may improve the cosmetic deformity and may help minimize or even improve the cardiopulmonary compromise. The 2 main surgical interventions are the Ravitch and Nuss procedures. Although superiorly of 1 approach has not been established, there is now more than 20 yr of successful experience with the minimally invasive Nuss procedure. For teenagers with exercise limitations, surgical repair may result in improved exercise tolerance. Normalization of lung perfusion scans and maximal voluntary ventilation have also been observed after surgery. Utilization of a magnetic brace with gradual remodeling of the pectus deformity is under clinical investigation. Ongoing treatment to address the secondary musculoskeletal findings is commonly employed before and after the operation.

Bibliography is available at Expert Consult.

### 417.2 Pectus Carinatum and Sternal Clefts

#### ETIOLOGY AND EPIDEMIOLOGY

Pectus carinatum is a sternal deformity accounting for 5-15% of congenital chest wall anomalies. Anterior displacements of the mid and lower sternum and adjacent costal cartilages are the most common types. They are most commonly associated with protrusion of the upper sternum; depression of the lower sternum occurs in only 15% of patients. Asymmetry of the sternum is common, and localized depression of the lower anterolateral chest is also often observed. Males are affected 4 times more often than females. There is a high familial occurrence and a common association of mild to moderate scoliosis. Mitral valve disease and coarctation of the aorta are associated with this anomaly. Three types of anatomic deformity occur (upper, lower, and lateral pectus carinatum), with corresponding physiologic changes and treatment algorithms.
Bibliography
Asphyxiating Thoracic Dystrophy (Thoracic-Pelvic-Phalangeal Dystrophy)

Steven R. Boas

**ETIOLOGY**
A multisystem autosomal recessive disorder, asphyxiating thoracic dystrophy results in a constricted and narrow rib cage. Also known as Jeune syndrome, the disorder is associated with a characteristic skeletal abnormalities as well as variable involvement of other systems, including renal, hepatic, neurologic, pancreatic, and retinal abnormalities (see Chapter 700).

**CLINICAL MANIFESTATIONS**
Most patients with this disorder die shortly after birth from respiratory failure, although less-aggressive forms have been reported in older children. For those who survive the neonatal period, progressive respiratory failure often ensues, owing to impaired lung growth, recurrent pneumonia, and atelectasis originating from the rigid chest wall.

**DIAGNOSIS**
Physical examination reveals a narrowed thorax that, at birth, is much smaller than the head circumference. The ribs are horizontal, and the child has short extremities. Chest radiographs demonstrate a bell-shaped chest cage with short, horizontal, flaring ribs and high clavicles.

**TREATMENT**
No specific treatment exists, although thoracoplasty to enlarge the chest wall and long-term mechanical ventilation has been tried. Rib-expanding procedures have resulted in improved survival.

**PROGNOSIS**
For some children with asphyxiating thoracic dystrophy, improvement in the bony abnormalities occurs with age. However, children younger than age 1 yr often succumb to respiratory infection and failure. Progressive renal disease often occurs with older children. Use of vaccines for influenza and other respiratory pathogens is warranted, as is aggressive use of antibiotics for respiratory infections.

Bibliography is available at Expert Consult.

Achondroplasia

Steven R. Boas

**ETIOLOGY**
Achondroplasia is the most common condition characterized by disproportionate short stature (see Chapter 696). This condition is inherited as an autosomal dominant disorder that results in disordered growth. Much has been learned about this disorder, including its genetic origins (95% of cases caused by mutations in the gene coding for fibroblast growth factor receptor type 3) and how to minimize its serious complications.

**CLINICAL MANIFESTATIONS**
Restrictive pulmonary disease, affecting <5% of children with achondroplasia who are younger than 3 yr, is more likely at high elevation. Recurrent infections, cor pulmonale, and dyspnea are commonly associated. There is an increased risk of obstructive sleep apnea or hypoventilation. Hypoxemia during sleep is a common feature. Onset of restrictive lung disease can begin at a very young age. On examination, the breathing pattern is rapid and shallow, with associated abdominal breathing. The anteroposterior diameter of the thorax is reduced. Special growth curves for chest circumference of patients with achondroplasia from birth to 7 yr are available. Three distinct phenotypes exist: phenotypic group 1 patients possess relative adenotonsillar hypertrophy, group 2 patients have muscular upper airway obstruction and progressive hydrocephalus, and group 3 patients have upper airway obstruction without hydrocephalus. Kyphoscoliosis may develop during infancy.

Bibliography is available at Expert Consult.
Bibliography


Bibliography


**DIAGNOSIS**

Pulmonary function tests reveal a reduced vital capacity that is more pronounced in males. The lungs are small but functionally normal. Sleep studies are recommended due to the high prevalence of sleep-disordered breathing. Chest radiographs demonstrate the decreased anteroposterior diameter along with anterior cupping of the ribs. The degree of foramen magnum involvement correlates with the extent of respiratory dysfunction.

**TREATMENT**

Treatment of sleep apnea, if present, is supportive (see Chapter 19). Physiotherapy and bracing may minimize the complications of both kyphosis and severe lordosis. Aggressive treatment of respiratory infections and scoliosis is warranted.

**PROGNOSIS**

The life span is normal for most children with this condition, except for the phenotypic groups with hydrocephalus or with severe cervical or lumbar spinal compression.

**417.5 Kyphoscoliosis: Adolescent Idiopathic Scoliosis and Congenital Scoliosis**  
*Steven R. Boas*

**ETIOLOGY**

Adolescent idiopathic scoliosis (AIS) is characterized by lateral bending of the spine (see Chapter 679). It commonly affects children during their teen years, as well as during periods of rapid growth. The cause is unknown. Congenital scoliosis is uncommon, affecting girls more than boys, and is apparent in the 1st yr of life (see Chapter 679.2).

**CLINICAL MANIFESTATIONS**

The pulmonary manifestations of scoliosis may include chest wall restriction, leading to a reduction in total lung capacity, abnormal gas exchange, and airway obstruction. The angle of scoliosis deformity has been correlated with the degree of lung impairment only for patients with thoracic curves. Vital capacity, forced expiratory volume in 1 sec (FEV1), work capacity, oxygen consumption, diffusion capacity, chest wall compliance, and partial pressure of arterial oxygen decrease as the severity of thoracic curve increases. These findings can be seen in even mild to moderate AIS (Cobb angle <30 degrees) but generally do not occur in other, nonthoracic curves. Respiratory compromise is often more severe in children younger than 5 yr of age with large scoliotic curves. Reduction in peripheral muscle function is associated with AIS through either intrinsic mechanisms or deconditioning. Severe impairment can lead to cor pulmonale or respiratory failure and can occur before age 20 yr. Children with severe scoliosis, especially boys, may have abnormalities of breathing during sleep, and the resultant periods of hypoxemia may contribute to the eventual development of pulmonary hypertension.

**DIAGNOSIS**

Physical examination and an upright, posteroanterior radiograph with subsequent measurement of the angle of curvature (Cobb technique) remain the gold standard for assessment of scoliosis. Curves >10 degrees define the presence of scoliosis. Lung volume, respiratory muscle strength, and exercise capacity determination are essential in assessing the degree of respiratory compromise associated with scoliosis.

**TREATMENT**

Depending on the extent of the curve and the degree of skeletal maturation, treatment options include reassurance, observation, bracing, and surgery (spinal fusion). Influenza vaccine should be administered, given the extent of pulmonary compromise that may coexist. Because vital capacity is a strong predictor for the development of respiratory failure in untreated AIS, surgical goals are to diminish the scoliotic curve, maintain the correction, and prevent deterioration in pulmonary function. Abnormalities of vital capacity and total lung capacity, exercise intolerance, and the rate of change of these variables over time should be taken into consideration for the timing of surgical correction. Preoperative assessment of lung function (i.e., lung volumes, oxygen consumption, muscle strength, ventilation/perfusion) may assist in predicting postsurgical pulmonary difficulties. Many patients undergoing surgical correction may be managed postoperatively without mechanical ventilation. Even patients with mild scoliosis may have pulmonary compromise immediately after spinal fusion, secondary to pain and a body cast that may restrict breathing and interfere with coughing. Children with a preoperative FEV1 <40% predicted are at risk for requiring prolonged postoperative mechanical ventilation. Rib-expanding procedures have been successful in severe cases of congenital scoliosis. Choice of surgical approach may also impact lung function postoperatively.

**417.6 Congenital Rib Anomalies**  
*Steven R. Boas*

**CLINICAL MANIFESTATIONS**

Isolated defects of the highest and lowest ribs have minimal clinical pulmonary consequences. Missing midthoracic ribs are associated with the absence of the pectoralis muscle (Poland syndrome), and lung function can become compromised. Associated kyphoscoliosis and hemivertebrae may accompany this defect. If the rib defect is small, no significant sequelae ensue. When the 2nd to 5th ribs are absent anteriorly, lung herniation and significant abnormal respiration ensue. The lung is soft and nontender and may be easily reducible on examination. Complicating sequelae include severe lung restriction (secondary to scoliosis), cor pulmonale, and congestive heart failure. Symptoms are often minimal but can cause dyspnea. Respiratory distress is rare in infancy.

**DIAGNOSIS**

Chest radiographs demonstrate the deformation and absence of ribs with secondary scoliosis. Most rib abnormalities are discovered as incidental findings on a chest film.

**TREATMENT**

If symptoms are severe enough to cause clinical compromise or significant lung herniation, then homologous rib grafting can be performed. Rib-expanding procedures are also of great value. A modified Nuss procedure has been utilized to correct associated chest wall anomalies with rib abnormalities. Adolescent girls with congenital rib anomalies may require cosmetic breast surgery.

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


The population of pediatric patients receiving long-term mechanical ventilatory support has increased in the United States and many other nations because of improvements in the treatment of acute respiratory failure and advancements in invasive (e.g., tracheostomy with mechanical ventilator) and noninvasive (e.g., mask continuous
positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) ventilation. Despite the growing population, less than 1% of patients admitted to pediatric intensive care units require long-term mechanical ventilation. Infants, children, and adolescents with disorders of central control of breathing, disease of the airways, residual lung disease after severe respiratory illness, persistent pulmonary hypertension, and neuromuscular disorders may experience hypercarbic and/or hypoxemic chronic respiratory failure. Generally, the respiratory failure can be attributed to a primary cause, although many children have multiple causative factors. Chronic respiratory failure can be defined as pulmonary insufficiency for a protracted period, usually 28 days or longer.

Patients are maintained on long-term ventilation for varying periods of time depending on the underlying pathology. Patients with reversible neuropathies (Guillain-Barré syndrome, neuropathy of critical illness), bronchopulmonary dysplasia, pulmonary hypertension, airway abnormalities, and congenital heart disease before or after surgical intervention require long-term ventilation as a bridge for full recovery. Patients with conditions such as central hypoventilation, progressive neuromuscular disease, and high quadriplegia may need ventilatory support indefinitely. The goals of long-term mechanical ventilation are to sustain and extend life, enhance the quality of life, reduce morbidity, improve physical and psychologic function, and enhance growth and development. These goals are often optimized in the home setting, which is the preferred site of discharge for children who are ventilator dependent. When social circumstances do not allow for a safe discharge to home, patients may be transferred to a highly skilled nursing facility for long-term care.

In an observational cohort analysis of 228 children enrolled in a home ventilation program 52% had chronic pulmonary disease, many with multiple comorbidities. Eventually 30% of children with chronic pulmonary disease were successfully weaned off ventilation and 19% died. Twenty-seven percent of the total population had neuromuscular disease, of which 6% were weaned off ventilation and 21% died. Twenty percent of the total population had central hypoventilation, of which 4% were weaned from ventilation and 24% died. Causes of death included progression of underlying chronic respiratory failure (34%), cardiac failure (21%), acute respiratory failure, tracheal bleeding and tracheal obstruction (8.5% each), and tracheostomy accident (2%). Regression analysis suggested that children with chronic pulmonary disease were more likely to successfully wean off mechanical ventilation than those children in the other two groups.

### 418.1 Neuromuscular Diseases

*Zehava L. Noah and Cynthia Etzler Budek*

Neuromuscular diseases (NMDs) of childhood include muscular dystrophies, metabolic and congenital myopathies, anterior horn cell disorders, peripheral neuropathies, and diseases that affect the neuromuscular junction. Decreased muscle strength and endurance resulting from neuromuscular disorders can affect any skeletal muscle, including muscles involved in respiratory function. Of particular concern are those muscles mediating upper airway patency, generation of cough, and lung inflation. Acute respiratory insufficiency is typically the most prominent clinical manifestation of several acute neuromuscular disorders, including high-level spinal cord injury, poliomyelitis, Guillain-Barré syndrome (see Chapter 616), and botulism (see Chapter 210). Respiratory dysfunction constitutes the leading cause of morbidity and mortality in progressive neuromuscular disorders (e.g., Duchenne muscular dystrophy [see Chapter 609], spinal muscular atrophy, congenital myotonic dystrophy, myasthenia gravis [see Chapter 612], and Charcot-Marie-Tooth disease [see Chapter 613]).

**PATHOGENESIS**

Early onset of NMD can lead to chest wall deformity and lung disease as a consequence of developmental factors. In infancy, the chest wall is very compliant with relatively stiff lungs and small airways. With progressive weakness of the intercostal muscles, the chest wall becomes even more compliant. Small airways have a tendency to become obstructed, leading to microatelectasis and decreased functional residual capacity. The compliant chest wall with initial sparing of diaphragm function leads to development of a small bell-shaped chest with depressed sternum, protruding abdomen, and paradoxical breathing, typically seen in spinal muscular atrophy (SMA) type 1. As the disease progresses, severe hypotonia develops, chest wall muscles shorten and lose elasticity, costosternal and costovertebral joints contract, and lung volumes decrease. Inspiratory and expiratory pressures subsequently decrease, expiratory pressures more so than inspiratory, causing ineffective cough and poor airway clearance. As the child with NMD ages, kyphoscoliosis commonly develops, increasing the severity of restrictive lung disease. Although central control of breathing remains normal, response to central chemoreceptors may decrease because of chronic hypercapnia.

### TREATMENT

Even though gene-targeted therapies are being developed for some NMDs, current interventions are primarily supportive rather than curative. Close surveillance through periodic review of the history and physical examination is critical. The development of personality and behavioral changes, such as irritability, decreased attention span, fatigue, and somnolence, may point to the presence of sleep-associated gas exchange abnormalities and sleep fragmentation. Changes in speech and voice characteristics, nasal flaring, and the use of accessory muscles at rest may indicate progressive muscle dysfunction and respiratory compromise. Although the frequency of periodic reevaluation needs to be tailored to the individual child, guidelines were developed for the Duchenne muscular dystrophy population; an abbreviated summary of such recommendations, applicable to all children with NMDs, is provided in Table 418-1.

Guidelines for evaluation and management of patients with SMA were developed on the basis of expert consensus. Four classifications of SMA, based on age of onset and level of function, are recognized (Table 418-2). Treatment of SMA is focused on level of function (non-sitter, sitter, or walker) rather than SMA type. Unlike patients with Duchenne muscular dystrophy, patients with SMA do not demonstrate correlation between pulmonary function and need for mechanical ventilation.

### Table 418-1

<table>
<thead>
<tr>
<th>Initial Evaluation and Follow-Up of Patients with Neuromuscular Disease</th>
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<tbody>
<tr>
<td><strong>INITIAL EVALUATION</strong></td>
</tr>
<tr>
<td>History/physical/anthropometrics</td>
</tr>
<tr>
<td>Lung function and maximal respiratory pressures (PFTs)</td>
</tr>
<tr>
<td>Arterial blood gases</td>
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<tr>
<td>Polysomnography*</td>
</tr>
<tr>
<td>Exercise testing (in selected cases)</td>
</tr>
<tr>
<td>If vital capacity &gt;60% predicted or maximal respiratory pressures &gt;60 cm H₂O</td>
</tr>
<tr>
<td>If vital capacity &lt;60% predicted or maximal respiratory pressures &lt;60 cm H₂O</td>
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</table>

*Please note that if polysomnography is not readily available, multichannel recordings including oronasal airflow, nocturnal oximetry, and end-tidal carbon dioxide levels may provide an adequate alternative.

CXR, chest x-ray; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PFT, pulmonary function test.
ventilatory support. Longitudinal monitoring for signs and symptoms of sleep-disordered breathing and ineffective airway clearance should be utilized to direct patient care.

Bibliography is available at Expert Consult.

### 418.2 Congenital Central Hypoventilation Syndrome

Zehava L. Noah, Cynthia Etzler Budek, and Debra E. Weese-Mayer

Congenital central hypoventilation syndrome (CCHS) is a clinically complex disorder of respiratory and autonomic regulation. In the classic case of CCHS, symptoms of alveolar hypoventilation are manifest in the newborn period and during sleep only—with diminished tidal volume and a typically monotonous respiratory rate with cyanosis and hypercarbia. In more severe cases of CCHS, the hypoventilation is manifest during wakefulness and sleep. And in the cases of later-onset CCHS (LO-CCHS), symptoms are manifest after 1 mo of age (and often into childhood and adulthood) but hypoventilation is typically during sleep only. CCHS and LO-CCHS are further characterized by ventilatory failure to properly respond to hypercarbia and hypoxia during wakefulness and sleep coupled with physiologic and/or anatomic autonomic nervous system (ANS) dysregulation (ANSD). Physiologic ANSD may include all organ systems affected by the ANS, specifically the respiratory, cardiac (sinus node pauses, asystole), sudomotor, vasomotor, ophthalmologic, neurologic, and enteric systems. The anatomic or structural ANSD includes Hirschsprung disease and tumors of neural crest origin (neuroblastoma, ganglioneuroma, or ganglioneuroblastoma). Diagnosis and management of individuals with CCHS and LO-CCHS have improved considerably, owing to greater knowledge in genetic testing, comprehensive care, and availability of monitoring technology for the home.

### GENETICS

Mutations in the paired-like homeobox 2B (PHOX2B) gene are the cause of CCHS. PHOX2B is essential to the embryologic development of the ANS from the neural crest, and is expressed in key regions that explain much of the CCHS phenotype. Individuals with CCHS are heterozygous for either a polyalanine repeat expansion mutation (PARM) in exon 3 of the PHOX2B gene (normal number of alanines 20 with normal genotype 20/20), such that individuals with CCHS have 24-33 alanines on the affected allele (genotype range is 20/24-20/33), or a non–PARM (NPARM) resulting from a missense, nonsense, frameshift, or stop codon mutation. Roughly 90-92% of the cases of CCHS have PARMs and the remaining 8-10% of cases have NPARMs. LO-CCHS cases have consistently had the 20/24 or 20/25 genotypes, or, occasionally, a very small NPARM. The specific type of PHOX2B mutation is clinically significant as it can help with anticipatory guidance in patient management. Less than 1% of CCHS cases will have a deletion of most of exon 3 or the entire PHOX2B gene, although the specific phenotype related to these large deletion mutations is not entirely clear. Stepwise clinical PHOX2B testing for probands with the CCHS phenotype is advised (step 1: fragment analysis (screening test); then if negative, step 2: sequen sequencing; then if negative, step 3: multiplex ligation-dependent probe amplification) to minimize expense and expedite confirmation of the diagnosis.

The majority of CCHS cases occur because of a de novo PHOX2B mutation, but up to 25% of children with CCHS inherit the mutation in an autosomal dominant manner from a seemingly asymptomatic parent who is mosaic for the PHOX2B mutation. Therefore, an individual with CCHS has a 50% chance of transmitting the mutation and resulting disease phenotype, to each offspring. Mosaic parents have up to a 50% chance of transmitting the PHOX2B mutation to each successive offspring. Genetic counseling is essential for family planning and for delivery room preparedness in anticipation of a CCHS birth. PHOX2B testing is advised for both parents of a child with CCHS to anticipate risk of recurrence in subsequent pregnancies and to determine if a parent has yet undiagnosed LO-CCHS. However, only fragment analysis PHOX2B testing (also known as the screening test) will identify low level somatic mosaicism (it will be missed by sequencing testing). At present, no clinical testing is available to determine germ-line mosaicism, but prenatal testing for PHOX2B mutation is clinically available (http://www.genetests.org) for families with a known PHOX2B mutation.

### Ventilator Dependence

A correlation between the PHOX2B genotype and ventilator dependence is reported. The greater the number of extra alanines, the more likely the need for continuous ventilatory support, at least among the most common PHOX2B PARM genotypes (20/25, 20/26, 20/27). Thus patients with the 20/25 genotype seldom require awake ventilatory support, although they do require support during sleep. Patients with the 20/26 genotype have variable awake support needs, and patients with the 20/27 genotype and those with NPARMs are likely to need continuous ventilatory support.

### Hirschsprung Disease

See Chapter 332.3.

Overall, 20% of children with CCHS also have Hirschsprung disease, and any infant or child with CCHS or LO-CCHS who presents with constipation should undergo rectal biopsy to screen for absence of ganglion cells. The type of PHOX2B mutation can help the primary physician anticipate which individuals are at higher risk. The frequency of Hirschsprung disease seems to increase with the longer polyanaline tracts (genotypes 20/27-20/33) and in those with NPARMs. Thus far only 1 infant with the 20/25 genotype has been reported to have Hirschsprung disease.

### Tumors of Neural Crest Origin

Tumors of neural crest origin are more frequent in patients with NPARMs (50%) than in those with PARMs (1%). These extracranial tumors are more often neuroblastomas in individuals with NPARMs, rather than ganglioneuromas and ganglioneuroblastomas, which have been described in patients with longer PARMs (20/29, 20/30, and 20/33 genotype only). Thus far only 1 infant with a PARM (20/33 genotype) has been reported to have a neuroblastoma.

### Cardiac Asystole

Transient, abrupt, and prolonged sinus pauses have been identified in patients with CCHS, necessitating implantation of cardiac pacemakers when the pauses are 3 sec or longer. Among patients with the PHOX2B mutation, nearly 25% have a 50% chance of transmitting thePHOX2B mutation to each sibling. Mosaic parents have up to a 50% chance of transmitting the PHOX2B mutation to each successive offspring. Genetic counseling is essential for family planning and for delivery room preparedness in anticipation of a CCHS birth. PHOX2B testing is advised for both parents of a child with CCHS to anticipate risk of recurrence in subsequent pregnancies and to determine if a parent has yet undiagnosed LO-CCHS. However, only fragment analysis PHOX2B testing (also known as the screening test) will identify low level somatic mosaicism (it will be missed by sequencing testing). At present, no clinical testing is available to determine germ-line mosaicism, but prenatal testing for PHOX2B mutation is clinically available (http://www.genetests.org) for families with a known PHOX2B mutation.

### Table 418-2 Clinical Classification of Spinal Muscular Atrophy

<table>
<thead>
<tr>
<th>SMA TYPE</th>
<th>AGE OF ONSET</th>
<th>HIGHEST FUNCTION</th>
<th>NATURAL AGE OF DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (severe)</td>
<td>0-6 mo</td>
<td>Never sits</td>
<td>&lt;2 yr</td>
</tr>
<tr>
<td>Type 2 (intermediate)</td>
<td>7-18 mo</td>
<td>Never stands</td>
<td>&lt;2 yr</td>
</tr>
<tr>
<td>Type 3 (mild)</td>
<td>Older than 18 mo</td>
<td>Stands and walks</td>
<td>Adult</td>
</tr>
<tr>
<td>Type 4 (adult)</td>
<td>Second or third decade</td>
<td>Walks during adult years</td>
<td>Adult</td>
</tr>
</tbody>
</table>

Bibliography

genotypes, 19% of those with the 20/26 genotype and 83% of those with the 20/27 genotype have heart beat pauses of 3 sec or longer. Children with the 20/25 genotype are not noted to have prolonged asystole, although 2 adults diagnosed with LO-CCHS demonstrated prolonged asystoles of 4-8 sec duration. Risk for sinus pauses among children with NPARMs is unknown at present.

**Autonomic Nervous System Dysregulation**

A higher number of polyalanine repeats among the PARMs is associated with an increased number of physiologic symptoms of ANSD. A higher frequency of anatomic ANSD findings is seen in individuals with CCHS who have NPARMs than in those who have PARMs. In addition, there is a spectrum of physiologic ANSD symptoms, including decreased heart rate variability, esophageal/gastric/colonic dysmotility, decreased pupillary response to light, reduced basal body temperature, altered distribution and amount of diaphoresis, and altered perception of anxiety.

**Facial Phenotype**

Children with CCHS and PARMs have a characteristic facies that is boxy in appearance, flattened on profile, and short relative to its width. The following five variables correctly predict 86% of CCHS cases: upper lip height, binocular width, upper facial height, nasal tip protrusion, and inferior inflection of the lateral one-third of the upper lip vermilion border (lip trait).

**Neuropathology**

Anatomic findings in the brains of individuals with CCHS from early MRI studies were unremarkable, and those from autopsies were inconsistent before 2003 when PHOX2B testing became clinically available. In a small cohort of adolescents with suspected CCHS, although without consistent PHOX2B mutation confirmation, neuropsychologic brainstem changes were identified by diffusion tensor imaging in structures known to mediate central chemosensitivity and to link a network of cardiovascular, respiratory, and affective responses. The neuroanatomic defects in CCHS are likely the result of focal PHOX2B (mis)expression coupled with sequelae of recurrent hypoxemia/hypercarbia in the subset of suboptimally managed patients. On the basis of rodent studies and functional MRI in humans, the following regions pertinent to respiratory control show PHOX2B expression in the pons and medulla of the brainstem: locus coeruleus, dorsal respiratory group, nucleus ambiguus, parafacial respiratory group, among other areas. Physiologic evidence suggests that the respiratory failure in these children is mostly based on defects in central mechanisms, but peripheral mechanisms (mainly carotid bodies) may also be important.

Patients with CCHS have deficient carbon dioxide sensitivity during wakefulness and sleep such that they do not respond with a normal increase in ventilation in either state nor do they arouse in response to hypercarbia and/or hypoxemia during sleep. During wakefulness, a subset of patients may respond sufficiently to avoid significant hypercarbia, but most individuals with CCHS have hyperventilation that is severe enough that hypercarbia is apparent in the resting awake state. Children with CCHS also have altered sensitivity to hypoxia while awake and asleep. A key feature of CCHS is the lack of respiratory distress or sense of asphyxia with physiologic compromise (hypercarbia and/or hypoxemia). This lack of responsiveness to hypercarbia and/or hypoxemia with subsequent respiratory failure does not seem to consistently improve with age. A subset of older children with CCHS may show an increase in ventilation (specifically increase in respiratory rate rather than increase in tidal volume) when they are exercised at various work rates, a response that is possibly secondary to neural reflexes from rhythmic limb movements—although the increase in minute ventilation is often insufficient to avoid physiologic compromise.

**CLINICAL MANIFESTATIONS**

Patients with CCHS usually present in the 1st few hr after birth. Most children are the products of uneventful pregnancies and are term infants with appropriate weight for gestational age; Apgar scores have been variable. The affected infants do not show signs of respiratory distress, but their shallow respirations and respiratory pauses (apnea) evolve to respiratory failure with apparent cyanosis in the 1st day of life. In neonates with CCHS, the PaCO$_2$ accumulates during sleep to very high levels, sometimes >90 mm Hg, and may decline to normal levels after the infants awaken. This problem becomes most apparent with failure of multiple attempts at extubation in an intubated neonate (who appears well with ventilatory support but in whom respiratory failure develops after removal of the support). However, the more severely affected infants hypoventilate awake and asleep; thus the previously described difference in PaCO$_2$ between states is not apparent. Often, the respiratory rate is higher in rapid eye movement sleep than in nonrapid eye movement sleep in individuals with CCHS.

LO-CCHS should be suspected in infants, children, and adults who have unexplained hypoventilation, especially subsequent to the use of anesthetic agents, sedation, acute respiratory illness, and potentially treated obstructive sleep apnea. These individuals may have other evidence of chronic hypoventilation, including pulmonary hypertension, polycythemia, elevated bicarbonate concentration, difficulty concentrating, and mild unexplained neurocognitive impairment. Besides treatment for the alveolar hypoventilation, children with CCHS require comprehensive physiologic evaluation and coordinated care to optimally manage associated abnormalities such as Hirschsprung disease, tumors of neural crest origin, symptoms of physiologic ANSD including cardiac asystole, among other findings (details provided in American Thoracic Society 2010 Statement on CCHS).

**DIFFERENTIAL DIAGNOSIS**

Testing should be performed to rule out primary neuromuscular, lung, and cardiac disease as well as an identifiable brainstem lesion that could account for the full constellation of symptoms characteristic of CCHS. Introduction of clinically available PHOX2B genetic testing allows for early and definitive diagnosis of CCHS. Because CCHS mimics many treatable and/or genetic diseases, the following disorders should be considered: X-linked myotubular myopathy, multimicinole disease, congenital myasthenic syndrome, altered airway or intrathoracic anatomy (diagnosis made with bronchoscopy and chest CT), diaphragm dysfunction (diagnosis made with diaphragm fluoroscopy), congenital cardiac disease, a structural hindbrain or brainstem abnormality (diagnosis made with MRI of the brain and brainstem), Möbius syndrome (diagnosis made with MRI of the brain and brainstem and neurologic examination), and specific metabolic diseases, such as Leigh syndrome, pyruvate dehydrogenase deficiency, and discrete carnitine deficiency. However the profound hypercarbia without respiratory distress during sleep will quickly lead the clinician to consider the diagnosis of CCHS or LO-CCHS.

**Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation**

Previously referred to as LO-CCHS with hypothalamic dysfunction, ROHHAD (rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) is a very rare disorder that was renamed to clarify that it is distinct from LO-CCHS (Chapter 47). The acronym describes the general sequence or “unfolding” of presenting symptoms, which can evolve over several years. The most dramatic and sentinel feature of ROHHAD is the rapid-onset weight gain (often >20 lb), which occurs over a 6-12 mo period in a seemingly normal young child. The diagnosis is based on clinical criteria that include onset of obesity and alveolar hypoventilation after the age of 1.5 yr (typically between 2 and 7 yr of age) and evidence of hypothalamic dysfunction as defined by 1 or more of the following findings: rapid-onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failure of response to growth hormone stimulation, corticotropin deficiency, and delayed/precocious puberty. Although it may not be apparent early in the course, all children with ROHHAD will develop hypoventilation. Considering the high prevalence of cardiorespiratory arrest and multisystem involvement, children with this disorder require coordinated comprehensive care with attention to development of hypoventilation (such as with repeated
physiologic recordings awake and asleep), initiation of supported ventilation, bradycardia (via Holter monitor), treatment of hypothalamic dysfunction (with involvement of an endocrinologist), tumors of neural crest origin (often ganglioneuromas or ganglioneuroblastomas; with involvement of an oncologist), and behavioral/intellectual decline (with annual neurocognitive testing and aggressive educational intervention). With meticulous management of the airway, breathing, and circulation, children with ROHHAD seem to stabilize and begin improvement in awake spontaneous breathing—though longitudinal studies are in a preliminary stage at present. Because of the high incidence of neural crest tumors, ROHHAD may be a paraneoplastic disorder.

Children with ROHHAD may present with obstructive sleep apnea (OSA) after development of obesity, but ROHHAD is distinct from OSA hypoventilation syndrome and obesity hypoventilation syndrome. The child with ROHHAD will go onto to severe hypoventilation despite intervention for the OSA. In children with exogenous obesity, the existence of obesity hypoventilation syndrome is controversial and is often referred to as OSA hypoventilation syndrome because it describes chronic OSA with resulting overnight hypercarbia, hypoxemia, and frequent arousals that lead to an altered set point of the central control of breathing (insensitivity to hypercarbia), awake hypoventilation, and daytime sleepiness. In children with OSA hypoventilation syndrome, treatment of the upper airway obstruction would be expected to result in complete resolution of hypoventilation and daytime sleepiness. In contrast, among children with ROHHAD the relief of upper airway obstruction unveils the central alveolar hypoventilation that requires lifelong ventilatory support. Both are distinguished from LO-CCHS by the absence of a CCHS-related PHOX2B mutation and the presence of (often morbid) obesity.

**MANAGEMENT**

**Supported Ventilation—Diaphragm Pacing**

Depending on the severity of respiratory control deficit, the individual with CCHS can have various means of artificial ventilation: non-invasive positive pressure ventilation or mechanical ventilation via tracheostomy (see Chapter 418.4). Diaphragm pacing offers another mode of supported ventilation; it involves bilateral surgical implantation of electrodes beneath the phrenic nerves, with connecting wires to subcutaneously implanted receivers. The external transmitter, which is much smaller and lighter in weight than a ventilator, sends a signal to flat donut-shaped antennae that are placed on the skin, over the subcutaneously implanted receivers. A signal travels from the external transmitter, ultimately, to the phrenic nerve to stimulate contraction of the diaphragm. A tracheostomy is typically required, at least initially, because the pacers induce a negative pressure on inspiration as a result of the contraction of the diaphragm being unopposed by pharyngeal dilation. Individuals with CCHS who are ventilator-dependent 24 hr/day are ideal candidates for diaphragm pacing to provide increased ambulatory freedom (without the “ventilator tether”) while they are awake; however, they still require mechanical ventilator support while they are asleep. This balance between awake pacing and asleep mechanical ventilation allows for a rest from phrenic nerve stimulation at night. A growing number of children and adults who require artificial ventilatory support during sleep only are now using diaphragm pacing, a more acceptable option since the introduction of thoracoscopic diaphragm pacer implantation and shortened recovery time postoperatively.

**Monitoring in the Home**

Home monitoring for individuals with CCHS and LO-CCHS is distinctly different from and more conservative than that for other children requiring long-term ventilation because those with CCHS lack innate ventilatory and arousal responses to hypoxemia and hypercarbia. In the event of physiologic compromise, other children are more likely to show clinical signs of respiratory distress. For children and adults with CCHS and LO-CCHS, the only means of determining adequate ventilation and oxygenation is with objective measures from a pulse oximeter, end-tidal carbon dioxide monitor, and close supervision of these values by a trained registered nurse in the home and at school. At a minimum, it is essential that individuals with CCHS have continuous monitoring with pulse oximetry and end-tidal carbon dioxide with registered nurse supervision during all sleep time. Ideally, this such monitoring should be present 24 hr per day because, even while awake, they are not able to sense or adequately respond to a respiratory challenge as may occur with ensuing respiratory illness, increased activity, or even the simple activity of eating. These recommendations apply to all CCHS and LO-CCHS patients regardless of the nature of their artificial ventilatory support—but especially those with diaphragm pacer as they have no intrinsic alarms in the diaphragm pacer device.

**418.3 Other Conditions**

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**MYELOMENINGOCELE WITH ARNOLD-CHIARI TYPE II MALFORMATION**

Arnold-Chiari type II malformation (see Chapter 591.11) is associated with myelomeningocele, hydrocephalus, and herniation of the cerebellar tonsils, caudal brainstem, and the fourth ventricle through the foramen magnum. Sleep-disordered breathing, including OSA and hypoventilation, has been reported. Direct pressure on the respiratory centers or brainstem nuclei, or increased intracranial pressure because of the hydrocephalus may be responsible. Vocal cord paralysis, apnea, hypoventilation, and bradyarrhythmias have also been reported. Patients with Arnold-Chiari type II malformation have blunted responses to hypercapnia, and to a lesser degree, hypoxia.

**Management**

An acute change in the ventilatory state of a patient with this malformation requires immediate evaluation. Consideration must be given to posterior fossa decompression and/or treatment of the hydrocephalus. If this treatment is unsuccessful in resolving central hypoventilation or apnea, tracheostomy and long-term mechanical ventilation should be considered.

**RAPID-ONSET OBESITY, HYPOTHALAMIC DYSFUNCTION, AND AUTONOMIC DYSREGULATION**

See Chapter 418.2.

**Obesity Hypoventilation Syndrome**

As its name implies, obesity hypoventilation syndrome is a syndrome of central hypoventilation during wakefulness in obese patients with sleep-disordered breathing. Although it was initially described mainly in adult obese patients, obese children have also demonstrated the syndrome. Sleep-disordered breathing is a combination of OSA, hypopnea, and/or sleep hypoventilation syndrome. Patients are hypercapnic with cognitive impairment, morning headache, and hypersomnia during the day. Chronic hypoxemia may lead to pulmonary hypertension and cor pulmonale.

Obesity is associated with reduced respiratory system compliance, increased airway resistance, reduced functional residual capacity, and increased work of breathing. Affected patients are unable to increase their respiratory drive in response to hypercapnia. Leptin may have a role in this syndrome. The sleep-disordered breathing leads to compensatory metabolic alkalosis. Because of the long half-life of bicarbonate, its elevation causes compensatory respiratory acidosis during wakefulness with elevated PaCO₂.

**Management**

The use of CPAP during sleep may be sufficient for many patients. Patients with hypoxemia may require BiPAP and supplemental oxygen. Tracheostomy may be considered for patients who do not tolerate mask ventilation.

Bibliography is available at Expert Consult.
Chapter 418  Chronic Severe Respiratory Insufficiency 2150.e1

Bibliography


ACQUIRED ALVEOLAR HYPOVENTILATION
Traumatic, ischemic, and inflammatory injuries to the brainstem, brainstem infarction, brain tumors, bulbar polio, and viral paraneoplastic encephalitis may also result in central hypoventilation.

OBSTRUCTIVE SLEEP APNEA
Epidemiology
Habitual snoring during sleep is extremely common during childhood. As many as 27% of children who snore are affected by OSA. The current obesity epidemic has affected the epidemiology of this condition. Peak prevalence is at 2–8 yr of age. The ratio between habitual snoring and OSA is 4:1 to 6:1.

Pathophysiology
OSA occurs when the luminal cross-sectional area of the upper airway is significantly reduced during inspiration. With increased airway resistance and reduced activation of pharyngeal dilators, negative pressure leads to upper airway collapse. The site of upper airway closure in children with OSA is at the level of tonsils and adenoids. The size of tonsils and adenoids increases throughout childhood up to 12 yr of age. Environmental irritants such as cigarette smoke or allergic rhinitis may accelerate the process. Reports now suggest that early viral infections may affect adenotonsillar proliferation.

Clinical Presentation
Snoring during sleep, behavioral disturbances, learning difficulties, excessive daytime sleepiness, metabolic issues, and cardiovascular morbidity may alert the parent or physician to the presence of OSA. Diagnosis is made with the help of airway radiograms and a polysomnogram.

Treatment
When adenotonsillar hypertrophy is suspected, a consultation with an ear, nose, and throat specialist for adenoidectomy and/or tonsillectomy may be indicated. For patients who are not candidates for surgical intervention or persist with OSA despite adenoidectomy and/or tonsillectomy, CPAP or BiPAP during sleep may alleviate the obstruction (see Chapter 19).

SPINAL CORD INJURY
Epidemiology
There are an estimated 11,000 new spinal cord injuries (SCIs) annually in the United States, with more than 50% resulting in quadriplegia. SCI is relatively rare in pediatric patients, with an incidence of 1-13% of all SCI patients. The incidence in infancy and early childhood is similar for boys and girls. The preponderance of SCI in adolescents is in males. Motor vehicle accidents, falls, sports injuries, and assaults are the main causes. SCI usually leads to lifelong disability.

Pathophysiology
Children with SCI have a disproportionately higher involvement of the upper cervical spine, high frequency of spinal cord injury without radiographic abnormality, delayed onset of neurologic deficits, and higher proportion of complete injury. Thus, there is a high likelihood in pediatric SCI of quadriplegia with intercostal muscle and/or diaphragmatic paralysis leading to respiratory failure.

Management
Immobilization and stabilization of the spine must be accomplished simultaneously with initial patient resuscitation. Children with high SCI typically require lifelong ventilation, so the decision to place a tracheostomy for chronic ventilatory support is usually made early in their course of treatment. Depending on the child’s age and general condition, diaphragmatic pacing may be considered. Often patients with diaphragmatic pacing need tracheostomy placement if there is dyssynchrony between pacing and glottal opening. Muscle spasms occur frequently in the SCI patient and are treated with muscle relaxants. Occasionally the muscle spasms involve the chest and present a serious impediment to ventilation. Continuous intrathoracic infusion of muscle relaxant via an implanted subcutaneous pump may be indicated (see Chapter 606.5).

METABOLIC DISEASE
Mucopolysaccharidoses
See Chapter 88.

Mucopolysaccharidoses are a group of progressive hereditary disorders that lack the lysosomal enzymes that degrade glycosaminoglycans. Incompletely catabolized mucopolysaccharides accumulate in connective tissue throughout the body. The inheritance is autosomal recessive except for Hunt syndrome, which is X-linked. The diagnosis is suggested by the presence of glycosaminuria and is confirmed by a lysosomal enzyme assay. I-cell disease mucolipidosis type II is an inherited lysosomal disorder with accumulation of mucolipids. Phenotypically, it is similar to mucopolysaccharidoses, but the age of onset is earlier and there is no mucopolysacchariduria. Mucopolysacharide deposits are frequently found in the head and neck and cause airway obstruction. Typically, the affected child has a coarse face and large tongue. Significant deposits are found in the adenoids, tonsils, and cartilage. Airway radiograms and a polysomnogram may help define the severity of the upper airway obstruction.

Treatment options have included enzyme replacement therapy and stem cell transplantation with limited success. Adenoidectomy and/or tonsillectomy may be indicated but surgery alone seldom solves the problem of airway obstruction. Noninvasive CPAP or BiPAP, or tracheostomy with ventilatory support may be helpful.

Dysplasias
Campomelic dysplasia (see Chapter 698) and thanatophoric dysplasia (see Chapter 696) affect rib cage size, shape, and compliance, leading to respiratory failure. Most patients with these disorders do not survive beyond early infancy. Tracheostomy and ventilation may prolong life.

Glycogenosis Type II
See Chapter 87.1.

Glycogenosis type II is an autosomal recessive disorder. Clinical manifestations include cardiomyopathy and generalized muscle weakness. Cardiac issues may include heart failure and arrhythmias. Muscle weakness leads to respiratory insufficiency and sleep–disordered breathing. Treatment includes emerging therapies such as enzyme replacement therapy, chaperone molecules, and gene therapy. Supportive therapy may consist of either noninvasive ventilation, or tracheostomy and mechanical ventilation. Cardiac medications, protein–rich nutrition, and judicious physical therapy are additional measures that can be utilized.

Severe Tracheomalacia and/or Bronchomalacia (Airway Malacia)
Conditions associated with airway malacia include tracheoesophageal fistula, innominate artery compression, and pulmonary artery sling after surgical repair (see Chapter 389). Patients with tracheobronchomalacia present with cough, lower airway obstruction, and wheezing. Diagnosis is made via bronchoscopy, preferably with the patient breathing spontaneously in order to evaluate dynamic airway function. Positive end-expiratory pressure titration during the bronchoscopy helps identify the ideal airway pressure required to maintain airway patency and prevent tracheobronchial collapse.

Neuropathy of Severe Illness
Children recuperating from severe illness in the intensive care unit often have neuromuscular weakness from suboptimal nutrition. This neuromuscular weakness can be devastating when coupled with the catabolic effects of severe illness and the residual effects of sedatives, analgesics, and muscle relaxants, particularly if corticosteroids were administered. Children with neuromuscular compromise have limited ability to increase ventilation and usually do so by increasing respiratory rate. Because of weakness, costal and sternal retractions may not be observed. Children with severe neuromyopathy may respond to increased respiratory load by becoming apneic. A look of panic, a
change in vital signs such as significant tachycardia or bradycardia, and cyanosis may be the only signs of impending respiratory failure.

HEMATOLOGIC STEM-CELL TRANSPLANTATION

Hematologic stem cell transplant (HSCT) is a life-saving therapy for patients with hematologic, oncologic, and immunologic conditions. Historically, outcomes for these patients have been poor. Lung dysfunction after HSCT is a serious and often fatal complication. Common causes of HSCT lung dysfunction include bacterial, viral, and/or fungal infections, posttransplant lymphoproliferative disorder, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, pulmonary cyto-lytic thrombi, engraftment syndrome, and bronchiolitis obliterans. Improvements in the management of HSCT have resulted in decreased graft-versus-host disease severity. Improved critical care practices, such as more in-depth diagnostic evaluation and lung-sparing ventilator strategies, have resulted in improved outcomes. Despite improved outcomes, a subset of HSCT patients will require chronic respiratory support for prolonged periods of time. In addition to post HSCT therapy, ongoing care may include noninvasive or invasive home ventilation, tracheostomy placement, diuretics, and supplemental nutrition.

MITOCHONDRIAL DISEASES

See Chapter 86.

Mitochondria are primarily responsible for the production of adenosine triphosphate. Mitochondrial diseases are a heterogeneous group of diseases in which adenosine triphosphate production is disrupted. Mitochondrial diseases are increasingly recognized and diagnosed in the pediatric population. Organs with high-energy requirements such as the neurons, and skeletal and cardiac muscles are particularly vulnerable. Although myopathy is the most frequently recognized presentation of mitochondrial disease, it is often part of a multisystem disease process. Neurologic complications include progressive proximal myopathy, kyphoscoliosis, dyskinesia, dystonia and spasticity, stroke, epilepsy, and visual and hearing impairment. Non-neurologic manifestations include cardiomyopathy, gastrointestinal dysmotility, gastroesophageal reflux, delayed gastric emptying, and pseudocyst.

Respiratory complications of mitochondrial disease are multifactorial. Muscle weakness, kyphoscoliosis, muscle spasms, and movement disorders may result in a restrictive pattern, and respiratory compromise. Additionally, dyscoordinated swallow and reflux may result in aspiration. In some mitochondrial diseases such as Leigh syndrome (see Chapter 86), central hypoventilation is an integral part of the disease. Supportive care for these patients may include noninvasive or invasive ventilation, tracheostomy placement, diuretics, appropriate nutrition, and dietary supplements.

Bibliography is available at Expert Consult.

418.4 Long-Term Mechanical Ventilation

Zehava L. Noah and Cynthia Etzler Budek

Many children with chronic severe respiratory insufficiency will benefit from long-term ventilatory support. The goals of chronic ventilation are to maintain normal oxygenation and ventilation, and to minimize the work of breathing. Caring for a child on long-term ventilatory support in the home is a complex, physically demanding, emotionally taxing, and expensive process for the family. It changes the family routine, priorities, and overall lifestyle, and may adversely affect intra-familial and extrafamilial relationships. The discharge process for a child likely to require long-term ventilatory support should start early in the hospitalization, before the child is medically stable and prior to transition to a portable ventilator that can be maintained in the home. The child’s disease prognosis is a critical factor to consider when deciding to initiate long-term ventilation. Children with degenerative neuromuscular disease, such as SMA type I, suffer from respiratory failure very early in life, often triggered by the first respiratory illness. Although some parents of children with SMA decide to provide only palliative end-of-life care (see Chapter 43), others choose long-term invasive or noninvasive ventilatory support. Young children with chronic lung disease and airway malacia have the potential to improve their pulmonary function and to wean successfully off the ventilator if provided with adequate ventilation, good nutrition, and measures to promote development and prevent further lung injury.

Successful home discharge depends on whether there are adequate resources in the community to support the family. Some hospital programs that transition children home on ventilators utilize professional nurses in the hospital to assist with round-the-clock care. This level of care depends on adequate funding as well as availability of nursing agencies with skilled nurses. Housing can be a significant barrier to discharge if the home lacks adequate space for the child and caretakers, equipment, and supplies, presents environmental safety issues, including building and electrical code violations, and/or requires extensive home modifications for mobility, including ramping and lifts.

Funding for home care is typically a challenge for this pediatric population. Even if they have private insurance, coverage for home care benefits is often very limited. In the United States, most states have public aid funds available to support the special needs of eligible children who are ventilator dependent, although the extent of coverage varies considerably across the country.

RESPIRATORY EQUIPMENT FOR HOME CARE

Modes of mechanical ventilation support are discussed in Chapter 71.1.

Noninvasive Equipment

Supplemental oxygen and positive pressure support can be administered by nasal cannula. The nasal cannula system has the ability to deliver heated, supersaturated, high-flow gases. There are a number of mechanical devices available for the delivery of CPAP and BiPAP. These devices attach to nasal and full-face masks or nasal pillows and are best suited for the treatment of OSA where ventilatory support is required for only a portion of the day, typically during sleep. Long-term use of mask ventilation in small children may result in mid-face dysplasia or pressure wounds. This type of ventilation has also been used in children with mild forms of respiratory insufficiency due to recurrent atelectasis and/or nocturnal hypventilation, as well as for palliation in more severely affected patients.

Rocker Bed

A rocker bed moves in a longitudinal seesaw motion at a set cycle rate. The child is secured to the bed with a strap across the body. Movement of the bed and gravitational pull promotes diaphragm movement. The rocker bed may be an option for children with mild neuromuscular weakness such as children recovering from Guillain-Barré syndrome. For safety reasons this device should not be placed in a home with toddlers or young children, who may get trapped in its rotating mechanism.

Cuirasse

The cuirasse is a negative-pressure device that resembles a hard turtle shell. It is a fiberglas piece that is custom fit over the child’s anterior chest and provides a tight seal. A hose attached to the cuirasse applies cycled negative pressure that lifts and releases the anterior chest wall. The cuirasse is suitable only for infants and children with mild neuromuscular weakness and pliable chest walls. A similar negative-pressure device utilizes a plastic bag that fits snugly around the chest and operates under the same principle as the cuirasse to lift and release the chest wall.

Iron Lung

The iron lung is a device that also applies negative pressure to the child’s body. The child is placed in the iron lung cylinder with his head
Bibliography
to these measures, intermittent positive ventilation devices may be a useful adjunct. Control of oral secretions can be achieved pharmacologically with anticholinergic drugs, localized injection of botulinum toxin (Botox), or surgical ligation of selected salivary ducts. In extreme cases, surgical tracheolaryngeal separation may be indicated. If thick, tenacious secretions are problematic, patient hydration and dosing of anticholinergic medication should be reviewed. Administration of nebulized dornase alfa or N-acetylcysteine, hypertonic saline, and/or sodium bicarbonate may be considered to thin secretions. In selected cases, bronchoscopy may be indicated for the removal of inspissated secretions and/or reexpansion of atelectatic pulmonary lobe or segment.

**Physical Therapy, Occupational Therapy, and Speech Therapy**

Therapies are very important in management of chronic respiratory failure. Potential goals for physical therapy are mobilization of the patient and strengthening of muscles, particularly truncal and abdominal muscles that are essential to pulmonary rehabilitation. Occupational therapy goals revolve around achieving or maintaining developmental milestones. Child life/developmental therapy focuses on provision of developmentally appropriate environmental stimulation and age-appropriate play. Speech therapy goals deal with oromotor skills for feeding and communication. Evaluation of swallow is a key component of therapy for children with chronic respiratory failure. Sign language is frequently utilized for communication because of delayed speech or hearing loss. Audiology specialists should be involved in the assessment of hearing, as there is a higher incidence of hearing loss in patients undergoing long-term ventilation.

**Infections**

Infections—tracheitis (see Chapter 385.2), bronchitis (see Chapter 391.2), and pneumonia (see Chapter 400)—are common in patients with chronic respiratory failure. Infections may be caused by community-acquired viruses (adenovirus, influenza, respiratory syncytial virus, parainfluenza, rhinovirus) or community- or hospital-acquired bacteria. Common pathogens are Gram-negative, highly antimicrobial-resistant pathogens that may cause further deterioration in pulmonary function. Bacterial infection is most likely in the presence of fever, deteriorating lung function (hypoxia, hypercarbia, tachypnea, and retractions), leukocytosis, and mucopurulent sputum. The presence of leukocytes and organisms on Gram stain of tracheal aspirate, as well as the visualization of new infiltrates on radiographs, may be consistent with bacterial infection.

Infection must be distinguished from tracheal colonization of bacteria, which is asymptomatic and associated with normal amounts of clear tracheal secretions. If infection is suspected, it must be treated with antibiotics, based on the culture and sensitivities of organisms recovered from the tracheal aspirate. Starting inhaled tobramycin and polymyxin E early may avert more serious infection. Antibiotics should be used judiciously to prevent further colonization with drug-resistant organisms. However, some patients who have recurrent infections may benefit from prophylaxis with inhaled antibiotics. Preventive measures are essential and include immunizations (influenza, pneumococcus, Haemophilus influenzae type b), passive immunity (respiratory syncytial virus), and good tracheostomy care.

**Monitoring**

A patient who is ventilated in the home must be electronically and/or physically monitored at all times. Infants and young children, children who are cognitively impaired, and children who are completely tracheostomy dependent for airway patency because of suprastomal obstruction must be under direct observation of the caregivers at all times. Caregivers should also closely monitor children whose pulmonary status is fragile or fluctuant. Continuous monitoring of $O_2$ saturation and heart rate is recommended during sleep, and either continuous or intermittent monitoring during the daytime, depending on patient stability. Patients with CCHS or pulmonary hypertension are particularly vulnerable to episodes of hypoxemia and/or hypercarbia, and
those with pulmonary hypertension are particularly susceptible to rapid drops in $O_2$ saturation.

Patients evaluated in pulmonary clinic for follow up should be monitored at each visit for heart rate, $O_2$ saturation, and transcutaneous and/or end-tidal $CO_2$ levels. Pulmonary function tests should be considered for those patients who are old enough and able to cooperate, usually after 5 yr of age. Serial echocardiograms should be obtained to monitor progression of pulmonary hypertension. Increased frequency of monitoring and surveillance are recommended for patients whose pulmonary status has improved and are in the process of weaning completely off ventilator support. A polysomnogram performed off the ventilator may be useful when total liberation from mechanical ventilation is being contemplated. In addition to physiologic parameters, patients must be monitored for signs of stress, agitation, and fatigue. Often these signs appear one or more days after the ventilator parameter changes.

**WEANING OFF VENTILATOR SUPPORT**

Patients recuperating from pulmonary disease, who are on stable ventilator settings with low positive end-expiratory pressure and minimal or no $O_2$ support, should be evaluated periodically for readiness to begin weaning from mechanical ventilation. Barriers to weaning may include residual lung disease, pulmonary hypertension, impaired central control of breathing, and muscle weakness. Weakness often has a multifactorial etiology. Factors such as underlying neuromuscular disease, use of sedatives, analgesics, steroids and muscle relaxants, and prolonged immobility, as well as utilization of mechanical ventilation, may downregulate mitochondrial activity in the respiratory muscles, and more so the diaphragm, and produce muscular changes resulting in weakness. Consequently, it is important to avoid 24 hr/day patient synchrony with ventilation and titrate the amount of ventilator support to prevent fatigue, yet facilitate spontaneous breathing.

When transitioning from full mechanical ventilatory support to spontaneous breathing, conditioning of the respiratory muscles can be achieved by several methods: gradual decrease of mechanical support by decreasing the ventilator pressures and/or rate, sprints of pressure support ventilation, retraining of the respiratory muscles with breathing exercises against an obstructed airway, and spontaneous breathing sprints off the ventilator. The weaning program may be initiated prior to initial hospital discharge or during follow up clinic visits. An initial weaning schedule may consist of 15 min sprints of free breathing off the ventilator up to 3 times/day while directly observed by caregiver and monitoring of respiratory parameters. The sprints are lengthened gradually with continued monitoring in the home and during frequent clinic visits. Additional factors that reflect tolerance of increased work of breathing, including weight gain, energy levels, general behavior and sleep patterns, are also monitored carefully. When the child has completely weaned off ventilator support while awake and is only on the ventilator approximately 6 hr nightly during sleep, a polysomnogram study performed off the ventilator may be considered prior to complete liberation from the mechanical ventilation device.

**DISCHARGE PROCESS**

The discharge process for a child going home for the first time on a ventilator is complex. A multidisciplinary, coordinated team approach is needed to develop an individualized, comprehensive plan that addresses medical, psychosocial, developmental, educational, and safety issues. The child should be transitioned to a ventilator suitable for home use that allows portability as well as adequate ventilation. Depending on the type of ventilation employed, a tracheostomy is typically placed to promote comfort and provide a stable airway as soon as the decision for long-term ventilation is made. Medical management should also focus on transitioning oxygen and ventilator parameters to settings appropriate for home care. The ventilated child must demonstrate medical stability at a level that can be safely managed at home; interventions to maintain patient stability should be minimal 1-2 wk before discharge.

Nutrition should be optimized to promote growth yet minimize excessive weight gain and carbon dioxide production. The nutritional requirements of a ventilated child are frequently decreased due to the supported work of breathing. The ventilated child often has problems with uncoordinated swallowing and oral aversion secondary to intubation. Speech therapy should be introduced early to begin oromotor therapy and return of swallow. Many children require gastrostomy tube placement to replace or supplement oral intake. Evaluation and management of reflux and the risk of aspiration should also be considered. Some children with severe reflux may require jejunal feedings. Communication devices to augment speech and introduction of sign language for speech and hearing impaired should be part of the planning.

Training of family caregivers should be initiated early in the discharge process and should be provided by nurses, respiratory care practitioners, and physical, occupational, and speech therapists knowledgeable in the individual child’s care. Home caregivers, typically the parents or family members and home nursing staff, are instructed in all aspects of the child’s care, including tracheostomy tube changes and care, tube feedings and care, medication administration, ventilator management and troubleshooting, emergency response, and cardiovascular pulmonary resuscitation. Caregiver independence in delivery of care at the bedside and while transporting the child should be emphasized. Special emphasis should be placed on safety and the appropriate response in the event of an emergency. A standardized emergency bag containing critical tracheostomy and ventilator supplies should accompany the child at all times. A minimum of 2 family members should complete instruction and demonstrate their competency by independently providing their child’s care for a 24-48 hr period prior to discharge.

Community agencies are identified for provision of home support services, typically including a nursing agency and equipment vendor. The nursing agency may provide private duty nursing services. Home care nurses should have pediatric tracheostomy and ventilator experience and be well versed in the individual child’s care before home discharge. An equipment vendor who can provide the ventilator, medical equipment and supplies, and maintenance/repair service should be selected. A care conference involving the hospital team, funding agency, home nursing agency, equipment vendor, and family caregivers should take place before discharge. The conference is critical for coordination of last-minute details and facilitation of a smooth transition to home.

**OUTPATIENT FOLLOW UP**

Provision of ongoing medical support to the child and family after discharge is essential. The primary care provider in the community has the central role in coordination of care, and provision of well-child, acute, and chronic care, with the exception of ventilatory management. Equally important is the establishment of lines of communication between the primary care provider and the pulmonary/critical care specialists managing ventilator care, and the provision of timely access for advice and troubleshooting during the intervals between respiratory multidisciplinary clinic visits.

The purpose of the respiratory multidisciplinary clinic is to monitor the patient’s progress, ensure that the ventilatory support is sufficient to promote growth and development and, when appropriate, to initiate or continue the ventilator weaning process. Physicians and/or advanced practice nurses who are well versed in ventilator care, typically pulmonary or critical care specialists, as well as respiratory care practitioners, evaluate the patient in clinic. Clinical nutrition, social work, and case management services should also be readily available.

The frequency of the clinic visits depends on the stability of the patient and the frequency of medical interventions needed to maintain clinical stability. A patient discharged from the hospital for the first time on a ventilator is typically evaluated in clinic within a month and may require monthly follow-up visits. Once the child is stable, the frequency decreases to every 3-6 mo. Older long-term patients who are no longer having major growth spurts are typically scheduled for annual visits. Patients who are actively weaning from the ventilator are seen more frequently. During the clinic visit respiratory monitoring is obtained while the child is on the ventilator and, if medically indicated,
off the ventilator, and repeated whenever ventilator adjustments are made. Whenever possible, readings obtained from home monitoring devices are compared with clinic monitoring to determine correlation. Recommendations regarding the child’s ventilator management are communicated to the primary care provider by letter or phone call after each clinic visit.

**TRANSITION OF CARE**

The pulmonary team initiates ongoing discussions regarding self-care responsibilities and transitioning of medical care to adult providers with the adolescent and his parents when the patient reaches the early teens. Discussion about self-care should take into consideration realistic expectations about the adolescent’s physical and cognitive capabilities. The actual transition of care occurs for most young adults at age 18-21 yr, and includes referral to an internist as well as an adult pulmonologist. Transition of medical care also includes transition from pediatric to adult support services for funding sources and nursing care. Ideally, an outpatient visit that includes current and future adult medical providers together is completed to facilitate communication and formally transition care.

*Bibliography is available at Expert Consult.*
Bibliography
Respiratory symptoms commonly originate from extrapulmonary processes. The respiratory system adapts to metabolic demands and is exquisitely responsive to cortical input; therefore, **tachypnea** is common in the presence of metabolic stress such as fever, whereas **dyspnea** may be related to anxiety. **Cough** most commonly arises from upper or lower respiratory tract disorders, but it can originate from the central nervous system, as with cough tic or psychogenic cough, and it can be a prominent symptom in children with gastroesophageal reflux disease. **Chest pain** does not commonly arise from pulmonary processes in otherwise healthy children but more often has a neuromuscular or inflammatory etiology. **Cyanosis** can be caused by cardiac or hematologic disorders, and **dyspnea** and **exercise intolerance** can have a number of extrapulmonary causes. These disorders may be suspected on the basis of the history and physical examination, or they may be considered in children in whom diagnostic studies have atypical findings or who show poor response to usual therapy. Table 419-1 lists more common causes of such symptoms.

**EVALUATION**

In the evaluation of a child or adolescent with respiratory symptoms, it is important to obtain a detailed past medical history, family history, and review of systems to evaluate the possibility of extrapulmonary origin. A comprehensive physical examination is also essential in obtaining clues to extrapulmonary disease.

Disorders of other organ systems, and many systemic diseases, can have significant respiratory system involvement. Although it is most common to encounter these complications in patients with known diagnoses, respiratory system disease is sometimes the sole or most prominent symptom at the time of presentation. Acute aspiration during feeding can be the presentation of neuromuscular disease in an infant who initially appears to have normal muscle tone and development. Complications can be life-threatening, particularly in immunocompromised patients. The onset of respiratory findings may be insidious; for example, pulmonary vascular involvement in patients with systemic vasculitis may appear as an abnormality in diffusing capacity of the lung for carbon monoxide before the onset of symptoms. Table 419-2 lists disorders that commonly have respiratory complications.

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<table>
<thead>
<tr>
<th>SIGN OR SYMPTOM</th>
<th>NONRESPIRATORY CAUSE(S)</th>
<th>PATHOPHYSIOLOGY</th>
<th>CLUES TO DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>Cardiac disease</td>
<td>Inflammation (pericarditis), ischemia (anomalous coronary artery, vascular disease)</td>
<td>Precordial pain, friction rub on examination; exertional pain, radiation to arm or neck</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Gastroesophageal reflux disease</td>
<td>Esophageal inflammation and/or spasm</td>
<td>Heartburn, abdominal pain</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Congenital heart disease Methemoglobinemia</td>
<td>Right-to-left shunt Increased levels of methemoglobin interfere with delivery of oxygen to tissues</td>
<td>Neonatal onset, lack of response to oxygen Drug or toxin exposure, lack of response to oxygen</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Toxin exposure, drug side effect, or overdose Anxiety, panic disorder</td>
<td>Variable, but often metabolic acidosis Increased respiratory drive and increased perception of respiratory efforts</td>
<td>Drug or toxin exposure confirmed by history or toxicology screen, normal oxygen saturation measured by pulse oximetry Occurs during stressful situation, other symptoms of anxiety or depression</td>
</tr>
</tbody>
</table>

Continued
**Bibliography**


Table 419-2 | Disorders with Frequent Respiratory Tract Complications

<table>
<thead>
<tr>
<th>UNDERLYING DISORDER(S)</th>
<th>RESPIRATORY COMPLICATIONS</th>
<th>DIAGNOSTIC TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune disorders</td>
<td>Pulmonary vascular disease, restrictive lung disease, pleural effusion (especially systemic lupus erythematosus), upper airway disease (Wegener granulomatosis)</td>
<td>Spirometry, lung volume determination, oximetry, diffusing capacity of the lung for carbon monoxide, chest radiography, upper airway endoscopy, and/or CT</td>
</tr>
<tr>
<td>Central nervous system disease (static or progressive)</td>
<td>Aspiration of oral or gastric contents</td>
<td>Chest radiography, videofluoroscopic swallowing study, esophageal pH probe, fiberoptic bronchoscopy</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Infection, bronchiectasis</td>
<td>Chest radiography, fiberoptic bronchoscopy, chest CT</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Pleural effusion, hepatopulmonary syndrome</td>
<td>Chest radiography, assessment of orthodeoxia</td>
</tr>
<tr>
<td>Malignancy and its therapies</td>
<td>Infiltration, metastasis, malignant or infectious effusion, parenchymal infection, graft-versus-host disease (bone marrow transplant)</td>
<td>Chest radiography, chest CT, fiberoptic bronchoscopy, lung biopsy</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>Hypoventilation, atelectasis, pneumonia</td>
<td>Spirometry, lung volume determination, respiratory muscle force measurements</td>
</tr>
<tr>
<td>Obesity</td>
<td>Restrictive lung disease, obstructive sleep apnea syndrome, asthma</td>
<td>Spirometry, lung volume determination, nocturnal polysomnography</td>
</tr>
</tbody>
</table>
Knowledge of the cellular and molecular mechanisms of cardiac development is necessary for understanding congenital heart defects and will be even more important in developing strategies for prevention, whether cell or molecular therapies or fetal cardiac interventional procedures. Cardiac defects have traditionally been grouped by common morphologic patterns: for example, abnormalities of the outflow tracts (conotruncal lesions such as tetralogy of Fallot and truncus arteriosus) and abnormalities of atrioventricular septation (primum atrial septal defect, complete atrioventricular canal defect). These morphologic categories may be revised or eventually supplanted by new categories as our understanding of the genetic basis of congenital heart disease progresses.

Bibliography is available at Expert Consult.

420.1 Early Cardiac Morphogenesis

In the early presomite embryo, the first identifiable cardiac progenitor cell clusters are arranged in the anterior lateral plate mesoderm on both sides of the embryo's central axis; these clusters form paired cardiac tubes by 18 days of gestation. The paired tubes fuse in the midline on the ventral surface of the embryo to form the primitive heart tube by 22 days. This straight heart tube is composed of an outer myocardial layer, an inner endocardium, and a middle layer of extracellular matrix known as the cardiac jelly. There are 2 distinct cell lineages: the primary heart field provides precursor cells for the left ventricle, whereas the secondary heart field provides precursors for the atria and right ventricle. Premyocardial cells, including epicardial cells and cells derived from the neural crest, continue their migration into the region of the heart tube. Regulation of this early phase of cardiac morphogenesis is controlled in part by the interaction of specific signaling molecules or ligands, usually expressed by 1 cell type, with specific receptors, usually expressed by another cell type. Positional information is conveyed to the developing cardiac mesoderm by factors such as retinoids (isoforms of vitamin A), which bind to specific nuclear receptors and regulate gene transcription. Migration of epithelial cells into the developing heart tube is directed by extracellular matrix proteins (such as fibronectin) interacting with cell surface receptors (the integrins). Other important regulatory molecules include bone morphogenetic protein 2 (BMP2); fibroblast growth factor 4 (FGF4); the transcription factors Nkx2.5, GATA4, Mesp1, and Mesp2; and members of the Wnt/b-catenin signaling pathway. The clinical importance of these ligands is revealed by the spectrum of cardiac teratogenic effects caused by the retinoid-like drug isotretinoin.

At approximately 22-24 days, the heart tube begins to bend ventrally and toward the right (see Fig. 420-1). The heart is the first organ to escape from the bilateral symmetry of the early embryo. Looping brings the future left ventricle leftward and in continuity with the sinus venosus (future left and right atria), whereas the future right ventricle is shifted rightward and in continuity with the truncus arteriosus (future aorta and pulmonary artery). This pattern of development explains the relatively common occurrence of the cardiac anomalies double-outlet right ventricle and double-inlet left ventricle and the extreme rarity of double-outlet left ventricle and double-inlet right ventricle (see Chapter 430.5). When cardiac looping is abnormal (situs inversus, heterotaxia), the incidence of serious cardiac malformations is high and there are usually associated abnormalities in the left-right (L-R) patterning of the lungs and abdominal viscera.

Potential mechanisms of cardiac looping include differential growth rates for myocytes on the convex vs the concave surface of the curve, differential rates of programmed cell death (apoptosis), and mechanical forces generated within myocardial cells via their actin cytoskeleton. The signal for this directionality is contained in a concentration gradient between the right and left sides of the embryo in the expression of critical signaling molecules. A number of signaling...
Bibliography
Srivastava D: Making or breaking the heart: from lineage determination to morphogenesis, Cell 126:1037–1048, 2006.
The heart tube now consists of several layers of myocardium and a single layer of endocardium separated by cardiac jelly, an acellular extracellular matrix secreted by the myocardium. Septation of the heart begins at approximately day 26 with the ingrowth of large tissue masses, the endocardial cushions, at both the atrioventricular and conotruncal junctions (see Fig. 420-1). These cushions consist of protrusions of cardiac jelly, which, in addition to their role in development, also serve a physiologic function as primitive heart valves. Endocardial cells dedifferentiate and migrate into the cardiac jelly in the region of the endocardial cushions, eventually becoming mesenchymal cells that will form part of the atrioventricular valves.

Complete septation of the atrioventricular canal occurs with fusion of the endocardial cushions. Most of the atrioventricular valve tissue pathways have been identified as regulators of this L-R asymmetry, including sonic hedgehog (SHH), transforming growth factor-β, nodal, and LR dynein. Interestingly, mice in which the LR dynein gene has been inactivated display random L-R orientation of the heart and abdominal viscera, with 50% of their hearts looping to the right and 50% looping to the left.

**420.3 Cardiac Septation**

Daniel Bernstein

When looping is complete, the external appearance of the heart is similar to that of a mature heart; internally, the structure resembles a single tube, although it now has several bulges resulting in the appearance of primitive chambers. The common atrium (comprising both the right and left atria) is connected to the primitive ventricle (future left ventricle) via the atrioventricular canal. The primitive ventricle is connected to the bulbus cordis (future right ventricle) via the bulboventricular foramen. The distal portion of the bulbus cordis is connected to the truncus arteriosus via an outlet segment (the conus).

The heart tube now consists of several layers of myocardium and a single layer of endocardium separated by cardiac jelly, an acellular extracellular matrix secreted by the myocardium. Septation of the heart begins at approximately day 26 with the ingrowth of large tissue masses, the endocardial cushions, at both the atrioventricular and conotruncal junctions (see Fig. 420-1). These cushions consist of protrusions of cardiac jelly, which, in addition to their role in development, also serve a physiologic function as primitive heart valves. Endocardial cells dedifferentiate and migrate into the cardiac jelly in the region of the endocardial cushions, eventually becoming mesenchymal cells that will form part of the atrioventricular valves.

Complete septation of the atrioventricular canal occurs with fusion of the endocardial cushions. Most of the atrioventricular valve tissue
is derived from the ventricular myocardium in a process involving undermining of the ventricular walls. Because this process occurs asymmetrically, the tricuspid valve annulus sits closer to the apex of the heart than the mitral valve annulus does. Physical separation of these 2 valves produces the atrioventricular septum, the absence of which is the primary common defect in patients with atrioventricular canal defects (see Chapter 426.5). If the process of undermining is incomplete, the right atrioventricular valve may not separate normally from the ventricular myocardium, a possible cause of Ebstein anomaly (see Chapter 430.7).

Septation of the atria begins at ≈30 days with growth of the septum primum downward toward the endocardial cushions (see Fig. 420-1). The orifice that remains is the ostium primum. The endocardial cushions then fuse and, together with the completed septum primum, divide the atrioventricular canal into right and left segments. A 2nd opening appears in the posterior portion of the septum primum, the ostium secundum, and it allows a portion of the fetal venous return to the right atrium to pass across to the left atrium. Finally, the septum secundum grows downward, just to the right of the septum primum. Together with a flap of the septum primum, the ostium secundum forms the foramen ovale, through which fetal blood passes from the inferior vena cava to the left atrium (see Chapter 421).

Septation of the ventricles begins at about embryonic day 25 with protrusions of endocardium in both the inlet (primitive ventricle) and outlet (bulbus cordis) segments of the heart. The inlet protrusions fuse into the bulboventricular septum and extend posteriorly toward the inferior endocardial cushion, where they give rise to the inlet and trabecular portions of the interventricular septum. Ventricular septal defects can occur in any portion of the developing interventricular septum (see Chapter 426.6). The outlet or conotruncal septum develops from ridges of cardiac jelly, similar to the atrioventricular cushions. These ridges fuse to form a spiral septum that brings the future pulmonary artery into communication with the posterior and leftward left ventricle. Differences in cell growth of the outlet septum lead to lengthening of the segment of smooth muscle beneath the pulmonary valve (conus), a process that separates the tricuspid and pulmonary valves. In contrast, disappearance of the segment beneath the aortic valve leads to fibrous continuity of the mitral and aortic valves. Defects in these processes are responsible for conotruncal and aortic arch defects (truncus arteriosus, tetralogy of Fallot, pulmonary atresia, double-outlet right ventricle, interrupted aortic arch), a group of cardiac anomalies often associated with deletions of the DiGeorge critical region of chromosome 22q11 (see Chapters 423 and 424). The transcription factor Tbx1 has been implicated as a candidate gene, which may be responsible for DiGeorge syndrome. Several genes have been implicated in valve formation, including Ptpn11, which encodes the tyrosine phosphatase Shp-2, and when present in a mutated form is one of the genes responsible for Noonan syndrome, associated with pulmonary valve stenosis; and NOTCH1, a regulator of cell differentiation that has been associated with aortic valve disease.

### 420.4 Aortic Arch Development

Daniel Bernstein

The aortic arch, head and neck vessels, proximal pulmonary arteries, and ductus arteriosus develop from the aortic sac, arterial arches, and dorsal aortae. When the straight heart tube develops, the distal outflow portion bifurcates into the right and left 1st aortic arches, which join the paired dorsal aortae (Fig. 420-2). The dorsal aortae will fuse to form the descending aorta. The proximal aorta from the aortic valve to the left carotid artery arises from the aortic sac. The 1st and 2nd arches largely regress by about 22 days, with the 1st aortic arch giving rise to the maxillary artery and the 2nd to the stapedial and hyoid arteries. The 3rd arches participate in the formation of the innominate artery and the common and internal carotid arteries. The right 4th arch gives rise to the innominate and right subclavian arteries, and the left 4th arch participates in formation of the segment of the aortic arch between

![Figure 420-2](image-url)
the left carotid artery and the ductus arteriosus. The 5th arch does not persist as a major structure in the mature circulation. The 6th arches join the more distal pulmonary arteries, with the right 6th arch giving rise to a portion of the proximal right pulmonary artery and the left 6th arch giving rise to the ductus arteriosus. The aortic arch between the ductus arteriosus and the left subclavian artery is derived from the left-sided dorsal aorta, whereas the aortic arch distal to the left subclavian artery is derived from the fused right and left dorsal aortae. Abnormalities in development of the paired aortic arches are responsible for right aortic arch, double aortic arch, and vascular rings (see Chapter 432.1).

420.5 Cardiac Differentiation

Daniel Bernstein

The process by which the totipotent cells of the early embryo become committed to specific cell lineages is differentiation. Precordial mesodermal cells differentiate into mature cardiac muscle cells with an appropriate complement of cardiac-specific contractile elements, regulatory proteins, receptors, and ion channels. Expression of the contractile protein myosin occurs at an early stage of cardiac development, even before fusion of the bilateral heart primordia. Differentiation in these early mesodermal cells is regulated by signals from the anterior endoderm, a process known as induction. Several putative early signaling molecules include fibroblast growth factor, activin, and insulin. Signaling molecules interact with receptors on the cell surface; these receptors activate 2nd messengers, which, in turn, activate specific nuclear transcription factors (GATA-4, MEF2, Nkx, bHLH, and the retinoic acid receptor family) that induce the expression of specific gene products to regulate cardiac differentiation. Some of the primary disorders of cardiac muscle, the cardiomyopathies, may be related to defects in some of these signaling molecules (see Chapter 439).

Developmental processes are chamber specific. Early in development, ventricular myocytes express both ventricular and atrial isoforms of several proteins, such as atrial natriuretic peptide (ANP) and myosin light chain (MLC). Mature ventricular myocytes do not express ANP and express only a ventricular-specific MLC 2v isoform, whereas mature atrial myocytes express ANP and an atrial-specific MLC 2a isoform. Heart failure (see Chapter 442), volume overload (see Chapters 426 and 428), and pressure overload hypertrophy (see Chapter 427) are associated with a recapitulation of fetal cell phenotypes in which mature myocytes reexpress fetal proteins. Because different isoforms have different contractile behavior (fast vs. slow activation, high vs. low adenosine triphosphatase activity), expression of different isoforms may have important functional consequences.

The extent to which stem cells can be made to differentiate into cardiac muscle cells is the focus of investigation in the field of regenerative cardiology. The demonstration that fully differentiated cardiac muscle cells (e.g., skin fibroblasts or peripheral blood mononuclear cells) can be reprogrammed into induced pluripotential stem cells and then differentiated into cardiomycocytes in vitro, has opened up many new avenues to study cardiovascular disease. Some investigators believe that there are precursor cells (cardiac stem cells) resident within the myocardium that can replace damaged myocytes, although at a rate too slow to be clinically useful. Scientists are working on trying to stimulate these cells with the proper regulatory factors, thus inducing them to regenerate damaged cardiac muscle. Others are investigating whether circulating stem cells, bone marrow–derived cells, or the factors they secrete can support cardiac regeneration. Eventually, stem cells grown on biomechanical scaffolds may be used to build a replacement ventricle for patients with hypoplastic left or right heart.

420.6 Developmental Changes in Cardiac Function

Daniel Bernstein

During development, the composition of the myocardium undergoes profound changes that result in an increase in the number and size of myocytes. During prenatal life, this process involves myocyte division (hyperplasia), whereas after the 1st few postnatal weeks, subsequent cardiac growth occurs mostly by an increase in myocyte size (hypertrophy). The myocytes themselves change shape from round to cylindrical, the proportion of myofibrils (which contain the contractile apparatus) increases, and the myofibrils become more regular in their orientation.

The plasma membrane (known as the sarcolemma in myocytes) is the location of the ion channels and transmembrane receptors that regulate the exchange of chemical information from the cell surface to the cell interior. Ion fluxes through these channels control the processes of depolarization and repolarization. Developmental changes have been described for the sodium-potassium pump, the sodium-hydrogen exchanger, and voltage-dependent calcium channels. As the myocyte matures, extensions of the sarcolemma develop toward the interior of the cell (the t-tubule system), which dramatically increases its surface area and enhances rapid activation of the myocyte. Regulation of the membrane’s α- and β-adrenergic receptors with development enhances the ability of the sympathetic nervous system to control cardiac function as the heart matures.

The sarcoplasmic reticulum (SR), a series of tubules surrounding the myofibrils, controls the intracellular calcium concentration. A series of pumps regulate calcium release to the myofibrils for initiation of contraction (ryanodine-sensitive calcium channel) and calcium uptake for initiation of relaxation (adenosine triphosphate–dependent SR calcium pump). In immature hearts, this SR calcium transport system is less well developed, and such hearts consequently have an increased dependence on transport of calcium from outside the cell for contraction. In a mature heart, the majority of the calcium to activate contraction comes from the SR. This developmental phenomenon may explain the sensitivity of the infant heart to sarcolemmal calcium channel blockers such as verapamil, which can result in a marked depression in contractility (see Chapter 435).

The major contractile proteins (myosin, actin, tropomyosin, and troponin) are organized into the functional unit of cardiac contraction, the sarcomere. Each has several isoforms that are expressed differentially by location (atrium vs. ventricle) and by developmental stage (embryo, fetus, newborn, adult).

Changes in myocardial structure and myocyte biochemistry result in easily quantifiable differences in cardiac function with development. Fetal cardiac function is less responsive to changes in both preload (filling volume) and afterload (systemic resistance). The most effective means of increasing ventricular function in a fetus is through increasing the heart rate. After birth and with further maturation, preload and afterload play an increasing role in regulating cardiac function. The rate of cardiac relaxation is also developmentally regulated. The decreased ability of the immature SR calcium pump to remove calcium from the contractile apparatus is manifested as a decreased ability of the fetal heart to enhance relaxation in response to sympathetic stimulation.
421.1 The Fetal Circulation

The human fetal circulation and its adjustments after birth are similar to those of other large mammals, although rates of maturation differ. In the fetal circulation, the right and left ventricles exist in a parallel circuit, as opposed to the series circuit of a newborn or adult (Fig. 421-1A). In the fetus, the placenta provides for gas and metabolite exchange. Because the lungs do not provide gas exchange, the pulmonary vessels are vasoconstricted, diverting blood away from the pulmonary circulation. Three cardiovascular structures unique to the fetus are important for maintaining this parallel circulation: the ductus venosus, foramen ovale, and ductus arteriosus.

The placenta is not as efficient an oxygen exchange organ as the lungs, so that umbilical venous Po2 (the highest level of oxygen provided to the fetus) is only about 30-35 mm Hg. Approximately 50% of the umbilical venous blood enters the hepatic circulation, whereas the rest bypasses the liver and joins the inferior vena cava via the ductus venosus, where it partially mixes with poorly oxygenated inferior vena cava blood derived from the lower part of the fetal body. This combined lower body plus umbilical venous blood flow (Po2 of ≈26-28 mm Hg) enters the right atrium and is preferentially directed by a flap of tissue at the right atrial-inferior vena caval junction, the eustachian valve, across the foramen ovale to the left atrium (see Fig. 421-1B). This is the major source of left ventricular blood flow, as pulmonary venous return is minimal. Left ventricular blood is then ejected into the ascending aorta where it supplies predominantly the fetal upper body and brain.

Fetal superior vena cava blood, which is considerably less oxygenated (Po2 of 12-14 mm Hg), enters the right atrium and preferentially flows across the tricuspid valve, rather than the foramen ovale, into the right ventricle. From the right ventricle, the blood is ejected into the pulmonary artery. Because the pulmonary arterial circulation is vasoconstricted, only approximately 5% of right ventricular outflow enters the lungs. The major portion of this blood bypasses the lungs and flows right-to-left through the ductus arteriosus into the descending aorta to perfuse the lower part of the fetal body, including providing flow to the placenta via the 2 umbilical arteries. Thus, the upper part of the fetal body (including the coronary and cerebral arteries and those to the upper extremities) is perfused exclusively from the left ventricle with blood that has a slightly higher Po2 than the blood perfusing the lower part of the fetal body, which is derived mostly from the right ventricle. Only a small volume of blood from the ascending aorta (10% of fetal cardiac output) flows all the way around the aortic arch (aortic isthmus) to the descending aorta.

The total fetal cardiac output—the combined output of both the left and right ventricles—is ≈450 mL/kg/min. Approximately 65% of descending aortic blood flow returns to the placenta; the remaining 35% perfuses the fetal organs and tissues. In the sheep fetus, where most of these circulatory pathways were studied, right ventricular output is approximately 2 times that of the left ventricle. In the human fetus, which has a larger percentage of blood flow going to the brain, right ventricular output is probably closer to 1.3 times left ventricular flow. Thus, during fetal life the right ventricle is not only pumping against systemic blood pressure but is also performing a greater volume of work than the left ventricle.

It has been postulated that blood flow is an important determinant of growth of fetal cardiac chambers, valves, and blood vessels. Thus, in...
the presence of a narrowing (stenosis) of an upstream structure such as the mitral valve, flow downstream into the left ventricle is limited and left ventricular growth may be compromised, leading to hypoplastic left heart syndrome (see Chapter 431.10). Similarly, stenosis of a downstream structure such as the aortic valve can similarly disrupt flow into the left ventricle and lead to hypoplastic left-heart syndrome. Fetal cardiac interventional treatments, currently experimental, are aimed at opening stenotic aortic valves in mid-gestation fetuses, and allowing more normal left ventricular growth.

421.2 The Transitional Circulation

Daniel Bernstein

At birth, mechanical expansion of the lungs and an increase in arterial PO\textsubscript{2} result in a rapid decrease in pulmonary vascular resistance. Concomitantly, removal of the low-resistance placental circulation leads to an increase in systemic vascular resistance. The output from the right ventricle now flows entirely into the pulmonary circulation, and because pulmonary vascular resistance becomes lower than systemic vascular resistance, the shunt through the ductus arteriosus reverses and becomes left to right. In the course of several days, the high arterial PO\textsubscript{2} constricts and eventually closes the ductus arteriosus, which eventually becomes the ligamentum arteriosum. The increased volume of pulmonary blood flow returning to the left atrium from the lungs increases left atrial volume and pressure sufficiently to close the flap of the foramen ovale functionally, although the foramen may remain probe patent for several years.

Removal of the placenta from the circulation also results in closure of the ductus venosus. The left ventricle is now coupled to the high-resistance systemic circulation, and its wall thickness and mass begin to increase. In contrast, the right ventricle is now coupled to the low-resistance pulmonary circulation, and its wall thickness and mass decrease. The left ventricle, which in the fetus pumped blood only to the upper part of the body and brain, must now deliver the entire systemic cardiac output (∼350 mL/kg/min), an almost 200% increase in output. This marked increase in left ventricular performance is achieved through a combination of hormonal and metabolic signals, including an increase in the level of circulating catecholamines and in the density of myocardial β-adrenergic receptors through which catecholamines have their effect.

When congenital structural cardiac defects are superimposed on these dramatic physiologic changes, they often impede this smooth transition and markedly increase the burden on the newborn myocardium. In addition, because the ductus arteriosus and foramen ovale do not close completely at birth, they may remain patent in certain congenital cardiac lesions. Patency of these fetal pathways may either provide a lifesaving pathway for blood to bypass a congenital defect (a patent ductus in pulmonary atresia or coarctation of the aorta or a foramen ovale in transposition of the great vessels) or present an additional stress to the circulation (patent ductus arteriosus in a premature infant, pathway for right-to-left shunting in infants with pulmonary hypertension). Therapeutic agents may either maintain these fetal pathways (prostaglandin E\textsubscript{1}) or hasten their closure (indomethacin).

421.3 The Neonatal Circulation

Daniel Bernstein

At birth, the fetal circulation must immediately adapt to extraterine life as gas exchange is transferred from the placenta to the lungs (see Chapter 101.1). Some of these changes are virtually instantaneous with the first breath, whereas others develop over a period of hours or weeks. With the onset of ventilation, pulmonary vascular resistance is markedly decreased as a consequence of both active (PO\textsubscript{2}-related) and passive (mechanical related) pulmonary vasodilation. In a normal neonate, closure of the ductus arteriosus and the fall in pulmonary vascular resistance decreases pulmonary arterial and right ventricular pressures. The largest decline in pulmonary resistance from the high fetal levels to the low “adult” levels in the human infant at sea level usually occurs within the 1st 2-3 days but may be prolonged for 7 days or more. Over the next several weeks of life, pulmonary vascular resistance decreases even further, secondary to a remodeling of the pulmonary vasculature, including thinning of the vascular smooth muscle and recruitment of new vessels. This decrease in pulmonary vascular resistance significantly influences the timing of the clinical appearance of many congenital heart lesions that are dependent on the relative levels of systemic and pulmonary vascular resistances. The left-to-right shunt through an large ventricular septal defect may be minimal in the 1st wk after birth when pulmonary vascular resistance is still high. As pulmonary resistance decreases in the next week or 2, the volume of the left-to-right shunt through the ventricular septal defect increases and eventually leads to symptoms of heart failure within the 1st mo or 2 of life.

Significant differences between the neonatal circulation and that of older infants include: (1) right-to-left or left-to-right shunting may persist across the patent foramen ovale; (2) in the presence of cardio-pulmonary disease, continued patency of the ductus arteriosus may allow left-to-right, right-to-left, or bidirectional shunting; (3) the neonatal pulmonary vasculature constricts more vigorously in response to hypoxemia, hypercapnia, and acidosis; (4) the wall thickness and muscle mass of the neonatal left and right ventricles are almost equal; and (5) newborn infants at rest have relatively high oxygen consumption, which is associated with relatively high cardiac output. The newborn cardiac output (approximately 350 mL/kg/min) falls in the 1st 2 mo of life to approximately 150 mL/kg/min and then more gradually to the normal adult cardiac output of approximately 75 mL/kg/min. Although fetal hemoglobin is beneficial to delivery of oxygen in the low P0\textsubscript{2} fetal circulation, the high percentage of fetal hemoglobin present in the newborn may actually interfere with delivery of oxygen to tissues in the high systemic P0\textsubscript{2}, neonatal circulation (see Chapter 101.1).

The foramen ovale is usually functionally closed by the 3rd mo of life, although it is possible to pass a probe through the overlapping flaps in a large percentage of children and in 15-25% of adults. Functional closure of the ductus arteriosus is usually complete by 10-15 hr in a normal neonate, although the ductus may remain patent much longer in the presence of congenital heart disease, especially when associated with cyanosis. In premature newborn infants, an evanescent systolic murm r with late accentuation or a continuous murmur may be audible, and in the context of respiratory distress syndrome, the presence of a patent ductus arteriosus should be suspected (see Chapter 101.3). The normal ductus arteriosus differs morphologically from the adjoining aorta and pulmonary artery in that the ductus has a significant amount of circularly arranged smooth muscle in its medial layer. During fetal life, patency of the ductus arteriosus appears to be maintained by the combined relaxant effects of low oxygen tension and endogenously produced prostaglandins, specifically prostaglandin E\textsubscript{2}. In a full-term neonate, oxygen is the most important factor controlling ductal closure. When the P0\textsubscript{2} of the blood passing through the ductus reaches about 50 mm Hg, the ductal wall begins to constrict. The effects of oxygen on ductal smooth muscle may be direct or mediated by its effects on prostaglandin synthesis. Gestational age also appears to play an important role; the ductus of a premature infant is less responsive to oxygen, even though its musculature is developed.

Bibliography is available at Expert Consult.

421.4 Persistent Pulmonary Hypertension of the Neonate (Persistence of Fetal Circulatory Pathways)

See Chapter 101.7.
Bibliography
Section 2
Evaluation of the Cardiovascular System

Chapter 422
History and Physical Examination
Daniel Bernstein

The importance of the history and physical examination cannot be overemphasized in the evaluation of infants and children with suspected cardiovascular disorders. Patients may require further laboratory evaluation and eventual treatment, or the family may be reassured that no significant problem exists. Although the ready availability of echocardiography may entice the clinician to skip these preliminary steps, an initial evaluation by a skilled cardiologist is preferred for several reasons: (1) a cardiac examination allows the cardiologist to guide the echocardiographic evaluation toward confirming or eliminating specific diagnoses, thereby increasing its accuracy; (2) because most childhood murmurs are innocent, evaluation by a pediatric cardiologist can eliminate unnecessary and expensive laboratory tests; and (3) the cardiologist’s knowledge and experience are important in reassuring the patient’s family and preventing unnecessary restrictions on healthy physical activity. An experienced pediatric cardiologist can differentiate an innocent murmur from serious congenital heart disease by history and physical alone with a high sensitivity and specificity.

HISTORY
A comprehensive cardiac history starts with details of the perinatal period including the presence of cyanosis, respiratory distress, or prematurity. Maternal complications such as gestational diabetes, teratogenic medications, systemic lupus erythematosus, or substance abuse can be associated with cardiac problems. If cardiac symptoms began during infancy, the timing of the initial symptoms should be noted to provide important clues about the specific cardiac condition.

Many of the symptoms of heart failure in infants and children are age specific. In infants, feeding difficulties are common. Inquiry should be made about the frequency of feeding and either the volume of each feeding or the time spent on each breast. An infant with heart failure will awaken for the next feeding after a brief time. This cycle continues around the clock and must be carefully differentiated from colic or other feeding disorders. Additional symptoms and signs include those of respiratory distress: rapid breathing, nasal flaring, cyanosis, and chest retractions. In older children, heart failure may be manifested as exercise intolerance, difficulty keeping up with peers during sports or the need for a nap after coming home from school, poor growth, or chronic abdominal complaints. Eliciting a history of fatigue in an older child requires questions about age-specific activities, including stair climbing, walking, bicycle riding, physical education class, and competitive sports; information should be obtained regarding more severe manifestations such as orthopnea and nocturnal dyspnea.

Cyanosis at rest is often overlooked by parents; it may be mistaken for a normal individual variation in color. Cyanosis during crying or exercise, however, is more often noted as abnormal by observant parents. Many infants and toddlers turn “blue around the lips” when crying vigorously or during breath-holding spells; this condition must be carefully differentiated from cyanotic heart disease by inquiring about inciting factors, the length of episodes, and whether the tongue and mucous membranes also appear cyanotic. Newborns often have cyanosis of their extremities (acrocyanosis) when undressed and cold; this response to cold must be carefully differentiated from true cyanosis, where the mucous membranes are also blue.

Chest pain is an unusual manifestation of cardiac disease in pediatric patients, although it is a frequent cause for referral to a pediatric cardiologist, especially in adolescents. Nonetheless, a careful history, physical examination, and, if indicated, laboratory or imaging tests will assist in identifying the cause of chest pain (Table 422-1). For patients with some forms of repaired congenital heart disease or those with a...

<table>
<thead>
<tr>
<th>Table 422-1</th>
<th>Differential Diagnosis of Chest Pain in Pediatric Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSCULOSKELETAL (COMMON)</td>
<td>Trauma (accidental, abuse)</td>
</tr>
<tr>
<td></td>
<td>Exercise, overuse injury (strain, bursitis)</td>
</tr>
<tr>
<td></td>
<td>Costochondritis (Tietze syndrome)</td>
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<tr>
<td></td>
<td>Herpes zoster (cutaneous)</td>
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<td></td>
<td>Pleurodynia</td>
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<td></td>
<td>Fibrositis</td>
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<td></td>
<td>Slipping rib</td>
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<tr>
<td></td>
<td>Percocordial catch</td>
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<tr>
<td></td>
<td>Sickle cell anemia vasoocclusive crisis</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis (rare)</td>
</tr>
<tr>
<td></td>
<td>Primary or metastatic tumor (rare)</td>
</tr>
<tr>
<td>PULMONARY (COMMON)</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Pleurisy</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Chronic cough</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
</tr>
<tr>
<td></td>
<td>Infarction (sickle cell anemia)</td>
</tr>
<tr>
<td></td>
<td>Foreign body</td>
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<tr>
<td></td>
<td>Embolism (rare)</td>
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<tr>
<td></td>
<td>Pulmonary hypertension (rare)</td>
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<tr>
<td></td>
<td>Tumor (rare)</td>
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<tr>
<td></td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>GASTROINTESTINAL (LESS COMMON)</td>
<td>Esophagitis (gastroesophageal reflux, infectious, pill)</td>
</tr>
<tr>
<td></td>
<td>Esophageal foreign body</td>
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<tr>
<td></td>
<td>Esophageal spasm</td>
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<tr>
<td></td>
<td>Cholecystitis</td>
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<tr>
<td></td>
<td>Subduralhegamic abscess</td>
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<tr>
<td></td>
<td>Perihepatitis (Fitz-Hugh-Curtis syndrome)</td>
</tr>
<tr>
<td></td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>CARDIAC (LESS COMMON)</td>
<td>Pericarditis</td>
</tr>
<tr>
<td></td>
<td>Postpericardiotomy syndrome</td>
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<tr>
<td></td>
<td>Endocarditis</td>
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<tr>
<td></td>
<td>Cardiomyopathy</td>
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<tr>
<td></td>
<td>Mitral valve prolapse</td>
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<td></td>
<td>Aortic or subaortic stenosis</td>
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<tr>
<td></td>
<td>Arrhythmias</td>
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<tr>
<td></td>
<td>Marfan syndrome (dissecting aortic aneurysm)</td>
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<tr>
<td></td>
<td>Kawasaki disease</td>
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<tr>
<td></td>
<td>Cocaine, sympathomimetic ingestion</td>
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<tr>
<td></td>
<td>Angina (familial hypercholesterolemia, anomalous coronary artery)</td>
</tr>
<tr>
<td>IDIOPATHIC (COMMON)</td>
<td>Anxiety, hyperventilation</td>
</tr>
<tr>
<td></td>
<td>Panic disorder</td>
</tr>
<tr>
<td>OTHER (LESS COMMON)</td>
<td>Spinal cord or nerve root compression</td>
</tr>
<tr>
<td></td>
<td>Breast-related pathologic condition (mastalgia)</td>
</tr>
<tr>
<td></td>
<td>Castleman disease (lymph node neoplasm)</td>
</tr>
</tbody>
</table>
Cardiac disease may be a manifestation of a known congenital malformation syndrome with typical physical findings (Table 422-2) or a manifestation of a generalized disorder affecting the heart and other organ systems (Table 422-3). Extracardiac malformations may be noted in 20–45% of infants with congenital heart disease. Between 5% and 10% of patients have a known chromosomal abnormality; the importance of genetic evaluation will increase as our knowledge of specific gene defects linked to congenital heart disease increases.

A careful family history may also reveal early (at age <50 yr) coronary artery disease or stroke (suggestive of familial hypercholesterolemia or thrombophilia), sudden death (suggestive of cardiomyopathy or familial arrhythmic disorder), generalized muscle disease (suggestive of 1 of the muscular dystrophies, dermatomyositis, or familial or metabolic cardiomyopathy), or 1st-degree relatives with congenital heart disease.

**GENERAL PHYSICAL EXAMINATION**

A general assessment of the patient is always the first part of the examination, with specific attention directed toward the presence of cyanosis, abnormalities in growth, chest wall abnormalities, and any evidence of respiratory distress. Although the murmur may be the most prominent part of the overall examination, any murmur must be placed in context of other physical findings. Frequently, associated findings, such as the quality of the pulses, the presence of a ventricular heave or thrill, or the splitting of the second heart sound, provide important clues to a specific cardiac diagnosis.

Accurate measurement of height and weight and plotting on a standard growth chart are important because both cardiac failure and chronic cyanosis can result in failure to thrive. Growth failure is manifested predominantly by poor weight gain; if length or head circumference is also affected, additional congenital malformations or metabolic disorders should be suspected.

Mild cyanosis may be too subtle for early detection, and clubbing of the fingers and toes is not usually manifested until late in the first year of life, even in the presence of severe arterial oxygen desaturation. Cyanosis is best observed over the nail beds, lips, tongue, and mucous membranes. Differential cyanosis, manifested as blue lower extremities and pink upper extremities (usually the right arm), is seen with right-to-left shunting across a ductus arteriosus in the presence of coarctation or an interrupted aortic arch. Circumoral cyanosis or blueness around the forehead may be the result of prominent venous plexuses in these areas, rather than decreased arterial oxygen saturation. The extremities of infants often turn blue when the infant is unwrapped and cold (acrocyanosis), and this condition can be distinguished from central cyanosis by examination of the tongue and mucous membranes.

**Heart failure** in infants and children usually results in some degree of hepatomegaly and occasionally splenomegaly. The sites of peripheral edema are age dependent. In infants, edema is usually seen around the eyes and over the flanks, especially on initially waking. Older children and teenagers manifest both periorbital edema and pedal edema. A not uncommon initial complaint in these older patients is that their clothes no longer fit.

The heart rate of newborn infants is rapid and subject to wide fluctuations (Table 422-4). The average rate ranges from 120–140 beats/min and may increase to 170+ beats/min during crying and activity or drop to 70–90 beats/min during sleep. As the child grows older, the average pulse rate decreases and may be as low as 40 beats/min at rest. Persistent tachycardia (>200 beats/min in neonates, 150 beats/min in infants, or 120 beats/min in older children), bradycardia, or an irregular heartbeat other than sinus arrhythmia requires investigation to exclude pathologic arrhythmias (see Chapter 435). Sinus arrhythmia can usually be distinguished by the rhythmic nature of the heart rate variations, occurring in concert with the respiratory cycle, and with a P wave before every QRS complex.

Careful evaluation of the character of the pulses is an important early step in the physical diagnosis of congenital heart disease. A wide pulse pressure with bounding pulses may suggest an aortic runoff lesion such as patent ductus arteriosus, aortic insufficiency, an arterial-venous communication, or increased cardiac output secondary to anemia, anxiety, or conditions associated with increased catecholamine or thyroid hormone secretion. The presence of diminished pulses in all extremities is associated with pericardial tamponade, left ventricular outflow obstruction, or cardiomyopathy. The radial and femoral pulses should always be palpated simultaneously. Normally, the femoral pulse should be appreciated immediately before the radial pulse. In infants with coarctation of the aorta, the femoral pulses may be decreased. However, in older children with coarctation of the aorta, blood flow to the descending aorta may channel through collateral vessels and results in the femoral pulse being palpable but delayed until after the radial pulse (radial-femoral delay).

**Blood pressure** should be measured in the legs as well as in the arms to be certain that coarctation of the aorta is not overlooked. Palpation of the femoral or dorsalis pedis pulse, or both, is not reliable alone to exclude coarctation. In older children, a mercury sphygmomanometer with a cuff that covers approximately two-thirds of the upper part of the arm or leg may be used for blood pressure measurement. A cuff that is too small results in falsely high readings, whereas a cuff that is too large records slightly decreased pressure. Pediatric clinical facilities should be equipped with 3, 5, 7, 12, and 18 cm cuffs to accommodate the large spectrum of pediatric patient sizes. The 1st Korotkoff sounds indicate systolic pressure. As cuff pressure is slowly decreased, the sounds usually become muffled before they disappear. Diastolic pressure may be recorded when the sounds become muffled (preferred) or when they disappear altogether; the former is usually slightly higher and the latter slightly lower than true diastolic pressure. For lower-extremity blood pressure determination, the stethoscope is placed over the popliteal artery. Ordinarily, the pressure recorded in the legs with the cuff technique is approximately 10 mm Hg higher than that in the arms.

In infants, blood pressure can be determined by auscultation, palpation, or an oscillometric (Dinamap) device that, when properly used, provides accurate measurements in infants as well as older children.

Blood pressure varies with the age of the child and is closely related to height and weight. Significant increases occur during adolescence, and many temporary variations take place before the more stable levels of adult life are attained. Exercise, excitement, coughing, crying, and struggling may raise the systolic pressure of infants and children as much as 40–50 mm Hg greater than their usual levels. Variability in blood pressure in children of approximately the same age and body build should be expected, and serial measurements should always be obtained when evaluating a patient with hypertension (Figs. 422-1 and 422-2).

Although of little use in infants, in cooperative older children, inspection of the jugular venous pulse wave provides information about central venous and right atrial pressure. The neck veins should be inspected with the patient sitting at a 90-degree angle. The external jugular vein should not be visible above the clavicles unless central venous pressure is elevated. Increased venous pressure transmitted to the internal jugular vein may appear as venous pulsations without visible distention; such pulsation is not seen in normal children reclining at an angle of 45 degrees. Because the great veins are in direct communication with the right atrium, changes in pressure and the volume of this chamber are also transmitted to the veins. The 1 exception occurs in superior vena cava obstruction, in which venous pulsatility is lost.

**CARDIAC EXAMINATION**

The heart should be examined in a systematic manner, starting with inspection and palpation. A precordial bulge to the left of the sternum with increased precordial activity suggests cardiac enlargement; such bulges can often best be appreciated by having the child lay supine with the examiner looking up from the child’s feet. A subternal thrust indicates the presence of right ventricular enlargement, whereas an apical heave is noted with left ventricular enlargement. A hyperdynamic precordium suggests a volume load such as that found with a large left-to-right shunt, although it may be normal in a thin patient.
### Table 422-2  Congenital Malformation Syndromes Associated with Congenital Heart Disease

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHROMOSOMAL DISORDERS</strong></td>
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</tr>
<tr>
<td>Trisomy 21 (Down syndrome)</td>
<td>Endocardial cushion defect, VSD, ASD</td>
</tr>
<tr>
<td>Trisomy 21p (cat eye syndrome)</td>
<td>Miscellaneous, total anomalous pulmonary venous return</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve</td>
</tr>
<tr>
<td>Trisomy 9</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>XXXXY</td>
<td>PDA, ASD</td>
</tr>
<tr>
<td>Penta X</td>
<td>PDA, VSD</td>
</tr>
<tr>
<td>Triploidy</td>
<td>ASD, PDA</td>
</tr>
<tr>
<td>XO (Turner syndrome)</td>
<td>Bicuspid aortic valve, coarctation of aorta</td>
</tr>
<tr>
<td>Fragile X</td>
<td>Mitral valve prolapse, aortic root dilatation</td>
</tr>
<tr>
<td>Duplicated 3q2</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Deletion 5p (cri du chat syndrome)</td>
<td>VSD, PDA, aortic stenosis</td>
</tr>
<tr>
<td>Deletion 10q</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Deletion 13q</td>
<td>VSD, TOF, conotruncal lesions*</td>
</tr>
<tr>
<td>Deletion 18q</td>
<td>VSD</td>
</tr>
<tr>
<td><strong>SYNDROME COMPLEXES</strong></td>
<td></td>
</tr>
<tr>
<td>CHARGE association (coloboma, heart, atresia choanae, retardation, genital, and ear anomalies)</td>
<td>VSD, ASD, PDA, TOF, endocardial cushion defect</td>
</tr>
<tr>
<td>DiGeorge sequence, CATCH 22 (cardiac defects, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia)</td>
<td>Aortic arch anomalies, conotruncal anomalies</td>
</tr>
<tr>
<td>Alagille syndrome (arteriohepatic dysplasia)</td>
<td>Peripheral pulmonic stenosis, PS, TOF</td>
</tr>
<tr>
<td>VATER association (vertebral, anal, tracheoesophageal, radial, and renal anomalies)</td>
<td>VSD, TOF, ASD, PDA</td>
</tr>
<tr>
<td>FAVS (facioauriculovertebral spectrum)</td>
<td>TOF, VSD</td>
</tr>
<tr>
<td>CHILD (congenital hemidysplasia with ichthyosiform erythroderma, limb defects)</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Mullibrey nanism (muscle, liver, brain, eye)</td>
<td>Pericardial thickening, constrictive pericarditis</td>
</tr>
<tr>
<td>Asplenia syndrome</td>
<td>Complex cyanotic heart lesions with decreased pulmonary blood flow, transposition of great arteries, anomalous pulmonary venous return, dextrocardia, single ventricle, single atrioventricular valve</td>
</tr>
<tr>
<td>Polysplenia syndrome</td>
<td>Acyanotic lesions with increased pulmonary blood flow, azygos continuation of inferior vena cava, partial anomalous pulmonary venous return, dextrocardia, single ventricle, common atrioventricular valve</td>
</tr>
<tr>
<td>PHACE syndrome (posterior brain fossa anomalies, facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, eye anomalies)</td>
<td>VSD, PDA, coarctation of aorta, arterial aneurysms</td>
</tr>
<tr>
<td><strong>TERATOCENIC AGENTS</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>PDA, peripheral pulmonic stenosis</td>
</tr>
<tr>
<td>Fetal hydantoin syndrome</td>
<td>VSD, ASD, coarctation of aorta, PDA</td>
</tr>
<tr>
<td>Fetal alcohol syndrome</td>
<td>ASD, VSD</td>
</tr>
<tr>
<td>Fetal valproate effects</td>
<td>Coarctation of aorta, hypoplastic left side of heart, aortic stenosis, pulmonary atresia, VSD</td>
</tr>
<tr>
<td>Maternal phenylketonuria</td>
<td>VSD, ASD, PDA, coarctation of aorta</td>
</tr>
<tr>
<td>Retinoic acid embryopathy</td>
<td>Conotruncal anomalies</td>
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<tr>
<td><strong>OTHERS</strong></td>
<td></td>
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<tr>
<td>Apert syndrome</td>
<td>VSD</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Carpenter syndrome</td>
<td>PDA</td>
</tr>
<tr>
<td>Conradi syndrome</td>
<td>VSD, PDA</td>
</tr>
<tr>
<td>Crouzon disease</td>
<td>PDA, coarctation of aorta</td>
</tr>
<tr>
<td>Cutis laxa</td>
<td>Pulmonary hypertension, pulmonic stenosis</td>
</tr>
<tr>
<td>de Lange syndrome</td>
<td>VSD</td>
</tr>
<tr>
<td>Ellis–van Creveld syndrome</td>
<td>Single atrium, VSD</td>
</tr>
<tr>
<td>Holt-Oram syndrome</td>
<td>ASD, VSD, 1st-degree heart block</td>
</tr>
<tr>
<td>Infant of diabetic mother</td>
<td>Hypertrophic cardiomyopathy, VSD, conotruncal anomalies</td>
</tr>
<tr>
<td>Kartagener syndrome</td>
<td>Dextrocardia</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome</td>
<td>ASD, VSD</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>Pulmonic stenosis, ASD, cardiomyopathy</td>
</tr>
<tr>
<td>Pallister-Hall syndrome</td>
<td>Endocardial cushion defect</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>VSD</td>
</tr>
<tr>
<td>Scimitar syndrome</td>
<td>Hypoplasia of right lung, anomalous pulmonary venous return to inferior vena cava</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>VSD, PDA</td>
</tr>
<tr>
<td>TAR syndrome (thrombocytopenia and absent radius)</td>
<td>ASD, TOF</td>
</tr>
<tr>
<td>Treacher Collins syndrome</td>
<td>VSD, ASD, PDA</td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>Supravalvular aortic stenosis, peripheral pulmonic stenosis</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; AV, aortic valve; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*Conotruncal includes TOF, pulmonary atresia, truncus arteriosus, and transposition of great arteries.
## Table 422-3  Cardiac Manifestations of Systemic Diseases

<table>
<thead>
<tr>
<th>SYSTEMIC DISEASE</th>
<th>CARDIAC COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFLAMMATORY DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Hypotension, myocardial dysfunction, pericardial effusion, pulmonary hypertension</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>Pericarditis, rarely myocarditis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Pericarditis, Libman-Sacks endocarditis, coronary arteritis, coronary</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>atherosclerosis (with steroids), congenital heart block</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Pulmonary hypertension, myocardial fibrosis, cardiomyopathy</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Cardiomyopathy, arrhythmias, heart block</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Coronary artery aneurysm and thrombosis, myocardial infarction, myocarditis, valvular insufficiency</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Granuloma, fibrosis, amyloidosis, biventricular hypertrophy, arrhythmias</td>
</tr>
<tr>
<td>Löffler hypereosinophilic syndrome</td>
<td>Arrhythmias, myocarditis</td>
</tr>
<tr>
<td></td>
<td>Endomyocardial disease</td>
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<td></td>
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<tr>
<td><strong>INBORN ERRORS OF METABOLISM</strong></td>
<td></td>
</tr>
<tr>
<td>Refsum disease</td>
<td>Arrhythmia, sudden death</td>
</tr>
<tr>
<td>Hunter or Hurler syndrome</td>
<td>Valvular insufficiency, heart failure, hypertension</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>Mitral insufficiency, coronary artery disease with myocardial infarction</td>
</tr>
<tr>
<td>Glycogen storage disease Ila (Pompe disease)</td>
<td>Short P-R interval, cardiomegaly, heart failure, arrhythmias</td>
</tr>
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<td>Carnitine deficiency</td>
<td>Heart failure, cardiomyopathy</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Coronary thrombosis</td>
</tr>
<tr>
<td>Alkaptonuria</td>
<td>Atherosclerosis, valvular disease</td>
</tr>
<tr>
<td>Morquio-Ullrich syndrome</td>
<td>Aortic incompetence</td>
</tr>
<tr>
<td>Scheie syndrome</td>
<td>Aortic incompetence</td>
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<td></td>
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<tr>
<td><strong>CONNECTIVE TISSUE DISORDERS</strong></td>
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<td>Arterial calcification of infancy</td>
<td>Calcinosis of coronary arteries, aorta</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Aortic and mitral insufficiency, dissecting aortic aneurysm, mitral valve prolapse</td>
</tr>
<tr>
<td>Congenital contractual arachnodactyly</td>
<td>Mitral insufficiency or prolapse</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Mitral valve prolapse, dilated aortic root</td>
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<tr>
<td>Osteogenesis imperfecta</td>
<td>Aortic incompetence</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>Peripheral arterial disease</td>
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<td></td>
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<tr>
<td><strong>NEUROMUSCULAR DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Duchenne dystrophy</td>
<td>Cardiomyopathy, heart failure</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Cardiac rhabdomyoma</td>
</tr>
<tr>
<td>Familial deafness</td>
<td>Occasionally arrhythmia, sudden death</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>Pulmonic stenosis, pheochromocytoma, coarctation of aorta</td>
</tr>
<tr>
<td>Riley-Day syndrome</td>
<td>Episodic hypertension, postural hypotension</td>
</tr>
<tr>
<td>Von Hippel-Lindau disease</td>
<td>Hemangiomas, pheochromocytomas</td>
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<td></td>
</tr>
<tr>
<td><strong>ENDOCRINE-METABOLIC DISORDERS</strong></td>
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</tr>
<tr>
<td>Graves disease</td>
<td>Tachycardia, arrhythmias, heart failure</td>
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<td>Hypothyroidism</td>
<td>Bradycardia, pericardial effusion, cardiomyopathy, low-voltage electrophysiology</td>
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<tr>
<td>Pheochromocytoma</td>
<td>Hypertension, myocardial ischemia, myocardial fibrosis, cardiomyopathy, right-sided</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>endocardial fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEMATOLOGIC DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>High-output heart failure, cardiomyopathy, pulmonary hypertension</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>High-output heart failure, hemochromatosis</td>
</tr>
<tr>
<td>Hemochromatosis (1° or 2°)</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>OTHERS</strong></td>
<td></td>
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<tr>
<td>Appetite suppressants (fenfluramine and dexfenfluramine)</td>
<td>Cardiac valvulopathy, pulmonary hypertension</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Familial dwarfism and nevi</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen syndrome</td>
<td>Prolonged QT interval, sudden death</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>Heart block</td>
</tr>
<tr>
<td>LEOPARD syndrome (lentiginosis)</td>
<td>Pulmonic stenosis, prolonged Q-T interval</td>
</tr>
<tr>
<td>Progeria</td>
<td>Accelerated atherosclerosis</td>
</tr>
<tr>
<td>Osler-Weber-Rendu disease</td>
<td>Arteriovenous fistula (lung, liver, mucous membrane)</td>
</tr>
<tr>
<td>Romano-Ward syndrome</td>
<td>Prolonged Q-T interval, sudden death</td>
</tr>
<tr>
<td>Wein-Marchesani syndrome</td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>Vascular sclerosis, cardiomyopathy</td>
</tr>
</tbody>
</table>

LEOPARD, multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitals, retardation of growth, sensorineural deafness.
Pulse Rates at Rest

<table>
<thead>
<tr>
<th>AGE</th>
<th>LOWER LIMITS OF NORMAL (beats/min)</th>
<th>AVERAGE (beats/min)</th>
<th>UPPER LIMITS OF NORMAL (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>70</td>
<td>125</td>
<td>190</td>
</tr>
<tr>
<td>1–11 mo</td>
<td>80</td>
<td>120</td>
<td>160</td>
</tr>
<tr>
<td>2 yr</td>
<td>80</td>
<td>110</td>
<td>130</td>
</tr>
<tr>
<td>4 yr</td>
<td>80</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>6 yr</td>
<td>75</td>
<td>100</td>
<td>115</td>
</tr>
<tr>
<td>8 yr</td>
<td>70</td>
<td>90</td>
<td>110</td>
</tr>
<tr>
<td>10 yr</td>
<td>70</td>
<td>90</td>
<td>110</td>
</tr>
<tr>
<td>GIRLS</td>
<td>BOYS</td>
<td>GIRLS</td>
<td>BOYS</td>
</tr>
<tr>
<td>12 yr</td>
<td>70</td>
<td>65</td>
<td>90</td>
</tr>
<tr>
<td>14 yr</td>
<td>65</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>16 yr</td>
<td>60</td>
<td>55</td>
<td>80</td>
</tr>
<tr>
<td>18 yr</td>
<td>55</td>
<td>50</td>
<td>75</td>
</tr>
</tbody>
</table>

A 3rd heart sound is best heard with the bell at the apex in mid-diastole. A 4th sound occurring in conjunction with atrial contraction may be heard just before the 1st heart sound in late diastole. The 3rd sound may be normal in an adolescent with a relatively slow heart rate, but in a patient with the clinical signs of heart failure and tachycardia, it may be heard as a gallop rhythm and may merge with a 4th heart sound, a finding known as a summation gallop. A gallop rhythm is attributed to poor compliance of the ventricle, and exaggeration of the normal 3rd sound is associated with ventricular filling.

Ejection clicks, which are heard in early systole, are usually caused by a mildly to moderately stenotic aortic or pulmonary valve or to a dilated ascending aorta or pulmonary artery. They are heard so close to the 1st heart sound that they may be mistaken for a split 1st sound. Aortic ejection clicks are best heard at the left middle to right upper sternal border and are constant in intensity. They occur in conditions in which the aortic valve is stenotic or the aorta is dilated (tetralogy of Fallot, truncus arteriosus). Pulmonary ejection clicks, which are associated with mild to moderate pulmonary stenosis, are best heard at the left middle to upper sternal border and vary with respirations, often disappearing with inspiration. Split 1st heart sounds are usually heard best at the lower left sternal border. A mid-systolic click heard at the apex, often preceding a late systolic murmur, suggests mitral valve prolapse.

Murmurs should be described according to their intensity, pitch, timing (systolic or diastolic), variation in intensity, time to peak intensity, area of maximal intensity, and radiation to other areas. Auscultation for murmurs should be carried out across the upper precordium, down the left or right sternal border, and out to the apex and left axilla. Auscultation should also always be performed in the right axilla and over both sides of the back. Systolic murmurs are classified as ejection, pansystolic, or late systolic according to the timing of the murmur in relation to the 1st and 2nd heart sounds. The intensity of systolic murmurs is graded from I to VI: I, barely audible; II, medium intensity; III, loud but no thrill; IV, loud with a thrill; V, very loud but still requiring positioning of the stethoscope at least partly on the chest; and VI, so loud that the murmur can be heard with the stethoscope off the chest. In patients who have undergone prior heart surgery, a murmur of grade IV or greater may be heard in the absence of a thrill.

Systolic ejection murmurs start a short time after a well-heard 1st heart sound, increase in intensity, peak, and then decrease in intensity; they usually end before the 2nd sound. In patients with severe pulmonary stenosis, however, the murmur may extend beyond the 1st component of the 2nd sound, thus obscuring it. Pansystolic or holosystolic murmurs begin almost simultaneously with the 1st heart sound and continue throughout systole, on occasion becoming gradually descending. It is helpful to remember that after closure of the atrioventricular valves (the 1st heart sound), a brief period occurs during which ventricular pressure increases but the semilunar valves remain closed (isovolumic contraction; see Fig. 422-3). Thus, pansystolic murmurs (heard during both isovolumic contraction and the ejection phases of systole) cannot be caused by flow across the semilunar valves because these valves are closed during isovolumic contraction. Pansystolic murmurs must therefore be related to blood exiting the contracting ventricle via either an abnormal opening (a ventricular septal defect) or atrioventricular (mitral or tricuspid) valve insufficiency. Systolic ejection murmurs usually imply increased flow or stenosis across one of the ventricular outflow tracts (aortic or pulmonic). In infants with rapid heart rates, it is often difficult to distinguish between ejection and pansystolic murmurs. If a clear and distinct 1st heart sound can be appreciated, the murmur is most likely ejection in nature.

A continuous murmur is a systolic murmur that continues or “spils” into diastole and indicates continuous flow, such as in the presence of a patent ductus arteriosus or other aortopulmonary communication. This murmur should be differentiated from a to-and-fro murmur, where the systolic component of the murmur ends at or before the 2nd sound and the diastolic murmur begins after semilunar valve closure (aortic or pulmonary stenosis combined with insufficiency). A late systolic murmur begins well beyond the 1st heart sound and continues until the end of systole. Such murmurs may be heard

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**Table 422-4**

<table>
<thead>
<tr>
<th>AGE</th>
<th>GIRLS</th>
<th>BOYS</th>
<th>GIRLS</th>
<th>BOYS</th>
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</thead>
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<tr>
<td>12 yr</td>
<td>70</td>
<td>65</td>
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<td>85</td>
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<tr>
<td>14 yr</td>
<td>65</td>
<td>60</td>
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<td>80</td>
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<tr>
<td>16 yr</td>
<td>60</td>
<td>55</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>18 yr</td>
<td>55</td>
<td>50</td>
<td>75</td>
<td>95</td>
</tr>
</tbody>
</table>

An overly silent precordium with a barely detectable apical impulse suggests pericardial effusion or severe cardiomyopathy but may be normal in an obese patient.

The relationship of the apical impulse to the midclavicular line is also helpful in the estimation of cardiac size: the apical impulse moves laterally and inferiorly with enlargement of the left ventricle. Right-sided apical impulses signify dextrocardia, tension pneumothorax, or left-sided thoracic space-occupying lesions (e.g., diaphragmatic hernia).

Thrills are the palpable equivalent of murmurs and correlate with the area of maximal auscultatory intensity of the murmur. It is important to palpate the suprasternal notch and neck for aortic bruits, which may indicate the presence of aortic stenosis or, when faint, pulmonary stenosis. Right lower sternal border and apical systolic thrills are characteristic of ventricular septal defect and mitral insufficiency, respectively. Diastolic thrills are occasionally palpable in the presence of atrioventricular valve stenosis. The timing and localization of thrills should be carefully noted.

Auscultation is an art that improves with practice. The diaphragm of the stethoscope is placed firmly on the chest for high-pitched sounds; a lightly placed bell is optimal for low-pitched sounds. The physician should initially concentrate on the characteristics of the individual heart sounds and their variation with respirations and later concentrate on murmurs. The patient should be supine, lying quietly, and breathing normally. The 1st heart sound is best heard at the apex, whereas the 2nd heart sound should be evaluated at the upper left and right sternal borders. The 1st heart sound is caused by closure of the atrioventricular valves (mitral and tricuspid); the 2nd sound is caused by closure of the semilunar valves (aortic and pulmonary) (Fig. 422-3).

During inspiration, the decrease in intrathoracic pressure results in increased filling of the right side of the heart, which leads to an increased right ventricular ejection time and thus delayed closure of the pulmonary valve; consequently, splitting of the 2nd heart sound increases during inspiration and decreases during expiration.

Often, the 2nd heart sound seems to be single during expiration. The presence of a normally split 2nd sound is strong evidence against the diagnosis of atrial septal defect, defects associated with pulmonary arterial hypertension, severe pulmonary valve stenosis, aortic and pulmonary atresia, and truncus arteriosus. Wide splitting is noted in atrial septal defect, pulmonary stenosis, Ebstein anomaly, total anomalous pulmonary venous return, and right bundle branch block. An accentuated pulmonic component of the 2nd sound with narrow splitting is a sign of pulmonary hypertension. A single 2nd sound occurs in pulmonary or aortic atresia or severe stenosis, truncus arteriosus, and, often, transposition of the great arteries.
after a mid-systolic click in patients with mitral valve prolapse and insufficiency.

Several types of diastolic murmurs (graded I-IV) can be identified. A decrescendo diastolic murmur is a blowing murmur along the left sternal border that begins with S2 and diminishes toward mid-diastole. When high-pitched, this murmur is associated with aortic valve insufficiency or pulmonary insufficiency related to pulmonary hypertension. When low-pitched, this murmur is associated with pulmonary valve insufficiency in the absence of pulmonary hypertension. A low-pitched decrescendo diastolic murmur is typically noted after surgical repair of the pulmonary outflow tract in defects such as tetralogy of Fallot or in patients with absent pulmonary valves. A rumbling mid-diastolic murmur at the left middle and lower sternal border may be due to increased blood flow across the tricuspid valve, such as occurs with an atrial septal defect or, less often, because of actual stenosis of this valve. When this murmur is heard at the apex, it is associated by increased flow across the mitral valve, such as occurs with large left-to-right shunts at the ventricular level (ventricular septal defects), at the great vessel level (patent ductus arteriosus, aortopulmonary shunts), or with increased flow because of mitral insufficiency. When an apical diastolic rumbling murmur is longer and is accentuated at the end of diastole (pre-systolic), it usually indicates anatomic mitral valve stenosis.

The absence of a precordial murmur does not rule out significant congenital or acquired heart disease. Congenital heart defects, some of which are ductal dependent, may not demonstrate a murmur if the ductus arteriosus closes. These lesions include pulmonary or tricuspid valve atresia and transposition of the great arteries. Murmurs may seem insignificant in patients with severe aortic stenosis, atrial septal defects, anomalous pulmonary venous return, atrioventricular septal defects, coarctation of the aorta, or anomalous insertion of a coronary artery. Careful attention to other components of the physical examination (growth failure, cyanosis, peripheral pulses, precordial impulse, heart sounds) increases the index of suspicion of congenital heart defects in these cases. In contrast, loud murmurs may be present in the absence of structural heart disease, for example, in patients with a large noncardiac arteriovenous malformation, myocarditis, severe anemia, or hypertension.

Many murmurs are not associated with significant hemodynamic abnormalities. These murmurs are referred to as functional, normal, insignificant, or innocent (the preferred term). During routine random auscultation, more than 30% of children may have an innocent murmur at one time in their lives; this percentage increases when auscultation is carried out under nonbasal circumstances (high cardiac output because of fever, infection, anxiety). The most common innocent murmur is a medium-pitched, vibratory or “musical,” relatively short systolic ejection murmur, which is heard best along the left lower and mid-sternal border and has no significant radiation to the apex, base, or back. It is heard most frequently in children between 3 and 7 yr of age. The intensity of the murmur often changes with respiration and position and may be attenuated in the sitting or prone position. Innocent pulmonic murmurs are also common in children and adolescents and originate from normal turbulence during ejection into the pulmonary artery. They are higher pitched, blowing, brief early systolic murmurs of grades I-II in intensity and are best detected in the 2nd left parasternal space with the patient in the supine position. Features suggestive of heart disease include murmurs that are pansystolic, grade III or higher, harsh, located at the left upper sternal border, and associated with an early or mid-systolic click or an abnormal 2nd heart sound.

A venous hum is another example of a common innocent murmur heard during childhood. Such hums are produced by turbulence of blood in the jugular venous system; they have no pathologic significance and may be heard in the neck or anterior portion of the upper part of the chest. A venous hum consists of a soft humming sound
heard in both systole and diastole; it can be exaggerated or made to disappear by varying the position of the head, or it can be decreased by lightly compressing the jugular venous system in the neck. These simple maneuvers are sufficient to differentiate a venous hum from the murmurs produced by organic cardiovascular disease, particularly a patent ductus arteriosus.

The lack of significance of an innocent murmur should be discussed with the child’s parents. It is important to offer complete reassurance because lingering doubts about the importance of a cardiac murmur may have profound effects on child-rearing practices, most often in the form of overprotectiveness. An underlying fear that a cardiac abnormality is present may negatively affect a child’s self-image and subtly influence personality development. The physician should explain that an innocent murmur is simply a “noise” and does not indicate the presence of a significant cardiac defect. When asked, “Will it go away?,” the best response is to state that because the murmur has no clinical significance, it does not matter whether it “goes away.” Parents should be warned that the intensity of the murmur might increase during febrile illnesses, a time when, typically, another physician examines the child. With growth, however, innocent murmurs are less well heard and often disappear completely. At times, additional studies may be indicated to rule out a congenital heart defect, but “routine” electrocardiographic, chest roentgenographic, and echocardiographic examinations should be avoided in well children with innocent murmurs.

Figure 422-3 Idealized diagram of the temporal events of a cardiac cycle.

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


Part XX ♦ The Cardiovascular System

Chapter 423

Laboratory Evaluation

423.1 Radiologic Assessment

Daniel Bernstein

The chest x-ray remains a highly valuable diagnostic tool and is often the first imaging study performed in a child suspected of having a cardiac defect. It can provide information about cardiac size and shape, pulmonary blood flow (vascularity), pulmonary edema, and associated lung and thoracic anomalies that may be associated with congenital syndromes (skeletal dysplasias, extra or deficient number of ribs, abnormal vertebrae, previous cardiac surgery).

The most frequently used measurement of cardiac size is the maximal width of the cardiac shadow in a posteroanterior chest film taken mid-inspiration. A vertical line is drawn down the middle of the sternal shadow, and perpendicular lines are drawn from the sternal line to the extreme right and left borders of the heart; the sum of the lengths of these lines is the maximal cardiac width. The maximal chest width is obtained by drawing a horizontal line between the right and left inner borders of the rib cage at the level of the top of the right diaphragm. When the maximal cardiac width is more than half the maximal chest width (cardiothoracic ratio >50%), the heart is usually enlarged.

Cardiac size should be evaluated only when the film is taken during inspiration with the patient in an upright position. A diagnosis of “cardiac enlargement” on expiratory or prone films is a common cause of unnecessary referrals and laboratory studies.

The cardiothoracic ratio is a less useful index of cardiac enlargement in infants than in older children because the horizontal position of the heart may increase the ratio to >50% in the absence of true enlargement. Furthermore, the thymus may overlap not only the base of the heart but also virtually the entire mediastinum, thus obscuring the true cardiac silhouette.

A lateral chest roentgenogram may be helpful in infants as well as in older children with pectus excavatum or other conditions that result in a narrow anteroposterior chest dimension. In these situations, the heart may appear small in the lateral view and suggest that the apparent enlargement in the posteroanterior projection was due to either the thymic image (anterior mediastinum only) or flattening of the cardiac chambers as a result of a structural chest abnormality.

In the posteroanterior view, the left border of the cardiac shadow consists of 3 convex shadows produced, from above downward, by the aortic knob, the main and left pulmonary arteries, and the left ventricle (Fig. 423-1). In cases of moderate to marked left atrial enlargement, the atrium may project between the pulmonary artery and the left ventricle. The outflow tract of the right ventricle does not contribute to the shadows formed by the left border of the heart. The aortic knob is not as easily seen in infants and children as in adults. The side of the aortic arch (left or right) can often be inferred as being opposite the side of the midline from which the air-filled trachea is visualized. This observation is important because a right-sided aortic arch is often present in cyanotic congenital heart disease, particularly in tetralogy of Fallot. Three structures contribute to the right border of the cardiac silhouette. In the view from above, they are the superior vena cava, the ascending aorta, and the right atrium.

Enlargement of cardiac chambers or major arteries and veins results in prominence of the areas in which these structures are normally outlined on the chest x-ray. In contrast, the electrocardiogram (ECG) is a more sensitive and accurate index of ventricular hypertrophy.

The chest roentgenogram is also an important tool for assessing the degree of pulmonary vascularity. Pulmonary overcirculation is usually
related pediatric ECGs.

In a newborn, the mean QRS frontal-plane axis normally lies in the range of +110 to +180 degrees. The right-sided chest leads reveal a larger positive (R) than negative (S) wave and may do so for months because the right ventricle remains relatively thick throughout infancy. Left-sided leads (V5 and V6) also reflect right-sided dominance in the early neonatal period, when the R:S ratio in these leads may be <1. A dominant R wave in V5 and V6, reflecting left ventricular forces, quickly becomes evident within the 1st few days of life (Fig. 423-3). Over the years, the QRS axis gradually shifts leftward, and the right ventricular forces slowly regress. Leads V1, V4R, and V5R display a prominent R wave until 6 mo to 8 yr of age. Most children have an R:S ratio >1 in lead V1 until they are 4 yr of age. The T waves are inverted in leads V1, V4R, and V5R during infancy and may remain so into the middle of the 2nd decade of life and beyond. The processes of right ventricular thinning and left ventricular growth are best reflected in the QRS-T pattern over the right precordial leads. The diagnosis of right or left ventricular hypertrophy in a pediatric patient can be made only with an understanding of the normal developmental physiology of these chambers at various ages until adulthood is reached. As the left ventricle becomes dominant, the ECG evolves to the characteristic pattern of older children (Fig. 423-4) and adults (Fig. 423-5).

**Ventricular hypertrophy** may result in increased voltage in the R and S waves in the chest leads. The height of these deflections is governed by the proximity of the specific electrode to the surface of the heart; by the sequence of electrical activation through the ventricles, which can result in variable degrees of cancellation of forces; and by hypertrophy of the myocardium. Because the chest wall in infants and children, as

**423.2 Electrocardiography**

**Daniel Bernstein**

**DEVELOPMENTAL CHANGES**

The marked changes that occur in cardiac physiology and chamber dominance during the perinatal transition (see Chapter 421) are reflected in the evolution of the ECG during the neonatal period. Because vascular resistance in the pulmonary and systemic circulations is nearly equal in a term fetus, the intrauterine work of the heart results in an equal mass of both the right and left ventricles. After birth, systemic vascular resistance rises when the placental circulation is eliminated, and pulmonary vascular resistance falls when the lungs expand. These changes are reflected in the ECG as the right ventricular wall begins to thin.

The ECG demonstrates these anatomic and hemodynamic features principally by changes in QRS and T-wave morphologic features. Commonly, a 13-lead ECG is performed in pediatric patients, including either lead V1,R or V1,R, which are important in the evaluation of right ventricular hypertrophy. On occasion, lead V1 is positioned too far leftward to reflect right ventricular forces accurately. This problem is

associated with left-to-right shunt lesions, whereas pulmonary under-circulation is associated with obstruction of the outflow tract of the right ventricle. The esophagus is closely related to the great vessels, and a barium esophagogram can help delineate these structures in the initial evaluation of suspected vascular rings, although this has largely been supplanted by CT. Echocardiographic examination best defines the morphologic features of intracardiac chambers, cardiac valves, and intracardiac shunts. CT is used as an adjunct to echo to evaluate extracardiac vascular morphology. MRI is used to quantitate ventricular volumes, cardiac function, and shunt and regurgitant fractions.

**Figure 423-1** Idealized diagrams showing normal position of the cardiac chambers and great blood vessels. IVC, inferior vena cava; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava. (Adapted and redrawn from Dotter CT, Steinberg I: Angiocardiographic Interpretation, Radiology 153:513, 1949.)

**Figure 423-2** Electrocardiogram in a normal neonate <24 hr of age. Note the dominant R wave and upright T waves in leads V1,R and V1 (V1,R paper speed = 50 mm/sec).
well as in adolescents, may be relatively thin, the diagnosis of ventricular hypertrophy should not be based on voltage changes alone.

The diagnosis of pathologic right ventricular hypertrophy is difficult in the 1st wk of life because physiologic right ventricular hypertrophy is a normal finding. Serial tracings are often necessary to determine whether marked right axis deviation and potentially abnormal right precordial forces or T waves, or both, will persist beyond the neonatal period (Fig. 423-6). In contrast, an adult electrocardiographic pattern (see Fig. 423-5) seen in a neonate suggests left ventricular hypertrophy. The exception is a premature infant, who may display a more "mature" ECG than a full-term infant (Fig. 423-7) as a result of lower pulmonary vascular resistance secondary to underdevelopment of the medial muscular layer of the pulmonary arterioles. Some premature infants display a pattern of generalized low voltage across the precordium.

The ECG should always be evaluated systematically to avoid the possibility of overlooking a minor, but important, abnormality. One approach is to begin with an assessment of rate and rhythm, followed by a calculation of the mean frontal-plane QRS axis, measurements of segment intervals, assessment of voltages, and, finally, assessment of ST and T-wave abnormalities.

**RATE AND RHYTHM**

A brief rhythm strip should be examined to assess whether a P wave always precedes each QRS complex. The P-wave axis should then be estimated as an indication of whether the rhythm is originating from the sinus node. If the atria are situated normally in the chest, the P wave should be upright in leads I and aVF and inverted in lead aVR. With atrial inversion (situs inversus), the P wave may be inverted in lead I. Inverted P waves in leads II and aVF are seen in low atrial, nodal, or junctional rhythms. The absence of P waves indicates a rhythm originating more distally in the conduction system. In this case, the morphologic features of the QRS complexes are important in differentiating a junctional (usually a narrow QRS complex) from a ventricular (usually a wide QRS complex) rhythm.

**P WAVES**

Tall (>2.5 mm), narrow, and spiked P waves are indicative of right atrial enlargement and are seen in congenital pulmonary stenosis,
Ebstein anomaly of the tricuspid valve, tricuspid atresia, and sometimes cor pulmonale. These abnormal waves are most obvious in leads II, V₅R, and V₁ (Fig. 423-8A). Similar waves are sometimes seen in thyrotoxicosis. Broad P waves, commonly bifid and sometimes biphasic, are indicative of left atrial enlargement (Fig. 423-8B). They are seen in some patients with large left-to-right shunts (ventricular septal defect [VSD], patent ductus arteriosus [PDA]) and with severe mitral stenosis or regurgitation. Flat P waves may be encountered in hyperkalemia.

QRS COMPLEX

Right Ventricular Hypertrophy

For the most accurate assessment of ventricular hypertrophy, pediatric ECGs should include the right precordial lead V₃R or V₄R, or both. The diagnosis of right ventricular hypertrophy depends on demonstration of the following changes (see Fig. 423-6): (1) a qR pattern in the right ventricular surface leads; (2) a positive T wave in leads V₃R-V₅R and V₁-V₃; between the ages of 6 days and 6 yr; (3) a monophasic R wave in V₃R, V₄R, or V₁; (4) an rsR' pattern in the right precordial leads with the 2nd R wave taller than the initial one; (5) age-corrected increased voltage of the R wave in leads V₁-R₄-V₄R or the S wave in leads V₅-V₆, or both; (6) marked right axis deviation (>120 degrees in patients beyond the newborn period); and (7) complete reversal of the normal adult precordial RS pattern. At least 2 of these changes should be present to support a diagnosis of right ventricular hypertrophy.

Abnormal ventricular loading can be characterized as either systolic (as a result of obstruction of the right ventricular outflow tract, as in pulmonic stenosis) or diastolic (as a result of increased volume load, as in atrial septal defects [ASDs]). These 2 types of abnormal loads result in distinct electrocardiographic patterns. The systolic overload pattern is characterized by tall, pure R waves in the right precordial leads. In older children, the T waves in these leads are initially upright and later become inverted. In infants and children <6 yr, the T waves in V₁-R₄-V₄R and V₁ are abnormally upright. The diastolic overload pattern (typically seen in patients with ASDs) is characterized by an rsR’ pattern (Fig. 423-9) and a slightly increased QRS duration (minor right ventricular conduction delay). Patients with mild to moderate pulmonary stenosis may also exhibit an rsR’ pattern in the right precordial leads.

Left Ventricular Hypertrophy

The following features indicate the presence of left ventricular hypertrophy (Fig. 423-10): (1) depression of the ST segments and inversion of the T waves in the left precordial leads (V₅, V₆, and V₁), known as a left ventricular strain pattern—these findings suggest the presence of a severe lesion; (2) a deep Q wave in the left precordial leads; and (3) increased voltage of the S wave in V₂ and V₃, or the R wave in V₅-V₆, or both. It is important to emphasize that evaluation of left ventricular hypertrophy should not be based on voltage criteria alone. The concepts of systolic and diastolic overload, though not always consistent, are also useful in evaluating left ventricular enlargement. Severe systolic overload of the left ventricle is suggested by straightening of the ST segments and inverted T waves over the left precordial leads; diastolic overload may result in tall R waves, a large Q wave, and normal T waves over the left precordium. Finally, an infant with an ECG that would be considered “normal” for an older child may, in fact, have left ventricular hypertrophy.

Bundle Branch Block

A complete right bundle-branch block may be congenital or may be acquired after surgery for congenital heart disease, especially when a right ventriculotomy has been performed, as in repair of the tetralogy of Fallot. Congenital left bundle-branch block is rare; this pattern is occasionally seen with cardiomyopathy. A bundle-branch block pattern may be indicative of a bypass tract associated with one of the preexcitation syndromes (see Chapter 435).

P-R and Q-T Intervals

The duration of the P-R interval shortens with increasing heart rate; thus, assessment of this interval should be based on age- and rate-corrected nomograms. A long P-R interval is diagnostic of a 1st-degree heart block, the cause of which may be congenital, postoperative,
inflammatory (myocarditis, pericarditis, Lyme disease, rheumatic fever), or pharmacologic (digitalis).

The duration of the Q-T interval varies with the cardiac rate; a corrected Q-T interval (Q-Tc) can be calculated by dividing the measured Q-T interval by the square root of the preceding R-R interval. A normal Q-Tc should be <0.45. It is often lengthened with hypokalemia and hypocalcemia; in the former instance, a U wave may be noted at the end of the T wave (Fig. 423-11). There are a number of medications that can also lengthen the Q-T interval. A congenitally prolonged Q-T interval (Fig. 423-12) may also be seen in children with one of the long Q-T syndromes. These patients are at high risk for ventricular arrhythmias, including a form of ventricular tachycardia known as torsades de pointes, and sudden death (see Chapter 435.5).

**ST SEGMENT AND T-WAVE ABNORMALITIES**

A slight elevation of the ST segment may occur in normal teenagers and is attributed to early repolarization of the heart. In pericarditis, irritation of the epicardium may cause elevation of the ST segment followed by abnormal T-wave inversion as healing progresses. Administration of digitalis is sometimes associated with sagging of the ST segment and abnormal inversion of the T wave.

Depression of the ST segment may also occur in any condition that produces myocardial damage or ischemia, including severe anemia, carbon monoxide poisoning, aberrant origin of the left coronary artery from the pulmonary artery, glycogen storage disease of the heart, myocardial tumors, and mucopolysaccharidoses. An aberrant origin of the left coronary artery from the pulmonary artery may lead to changes indistinguishable from those of acute myocardial infarction in adults. Similar changes may occur in patients with other rare abnormalities of the coronary arteries and in those with cardiomyopathy, even in the presence of normal coronary arteries. These patterns are often misread in young infants because of the unfamiliarity of pediatricians with this “infarct” pattern, and thus a high index of suspicion must be maintained in infants with dilated cardiomyopathy or with symptoms compatible with coronary ischemia (e.g., inconsolable crying).

T-wave inversion may occur in myocarditis or pericarditis, or it may be a sign of either right or left ventricular hypertrophy and strain. Hypothyroidism may produce flat or inverted T waves in association with generalized low voltage. In hyperkalemia, the T waves are commonly of high voltage and are tent-shaped (Fig. 423-13).

**423.3 Hematologic Data**

_Daniel Bernstein_

In acyanotic infants with large left-to-right shunts, the onset of heart failure often coincides with the nadir of the normal physiologic anemia of infancy. Increasing the hematocrit in these patients to >40% may decrease shunt volume and result in an improvement in symptoms; however, this form of treatment is generally reserved for infants who are not otherwise surgical candidates (extremely premature infants or those with exceedingly complex congenital heart disease for whom only palliative surgery is possible). In these select infants, regular evaluation of the hematocrit and booster transfusions when appropriate may be helpful in improving growth.

Polycthemia is frequently noted in cyanotic patients with right-to-left shunts. Patients with severe polycythemia are in a delicate balance between the risks of intravascular thrombosis and a bleeding diathesis. The most frequent abnormalities include accelerated fibrinolysis, thrombocytopenia, abnormal clot retraction, hypofibrinogenemia, prolonged prothombin time, and prolonged partial thromboplastin time. The preparation of cyanotic, polycythemic patients for elective noncardiac surgery, such as dental extraction, includes evaluation and treatment of abnormal coagulation.

Because of the high viscosity of polycythemic blood (hematocrit >65%), patients with cyanotic congenital heart disease are at risk for the development of vascular thromboses, especially of cerebral veins. Dehydration increases the risk of thrombosis, and thus adequate fluid intake must be maintained during hot weather or intercurrent gastrointestinal illnesses. Diuretics should be used with caution in these patients and may need to be decreased if fluid intake is a concern. Polycythemic infants with concomitant iron deficiency are at even greater risk for cerebrovascular accidents, probably because of the decreased deformability of microcytic red blood cells. Iron therapy may reduce this risk somewhat, but surgical treatment of the cardiac anomaly is the best therapy.

Severely cyanotic patients should have periodic determinations of hemoglobin and hematocrit. Increasing polycythemia, often associated with headache, fatigue, dyspnea, or a combination of these conditions, is one indication for palliative or corrective surgical intervention. In cyanotic patients with inoperable conditions, partial exchange
Bibliography


transfusion may be required to treat asymptomatic individuals whose hematocrit has risen to the 65-70% level. This procedure is not without risk, especially in patients with an extreme elevation in pulmonary vascular resistance. Because these patients do not tolerate wide fluctuations in circulating blood volume, blood should be replaced with fresh-frozen plasma or albumin.

### 423.4 Echocardiography

Daniel Bernstein

Transthoracic echocardiography has replaced invasive studies such as cardiac catheterization for the initial diagnosis of most forms of congenital heart disease. The echocardiographic examination can be used to evaluate cardiac structure in congenital heart lesions, estimate intracardiac pressures and gradients across stenotic vessels and valves, quantitate cardiac contractile function (both systolic and diastolic), determine the direction of flow across a defect, examine the integrity of the coronary arteries, and detect the presence of vegetations from endocarditis, as well as the presence of pericardial fluid, cardiac tumors, and chamber thrombi. Echocardiography may also be used to assist in the performance of interventional procedures, including pericardiocentesis, balloon atrial septostomy (see Chapter 431.2), atrial or VSD closure and endocardial biopsy, and in the placement of flow-directed pulmonary artery (Swan-Ganz) monitoring catheters. Transthoracic echocardiography is used routinely to monitor ventricular function in patients during surgical procedures and can provide an immediate assessment of the results of surgical repair of congenital heart lesions. A complete transthoracic echocardiographic examination usually entails a combination of M-mode and 2-dimensional (2D) imaging, as well as pulsed, continuous, and color Doppler flow studies. Doppler tissue imaging provides a more quantitative assessments of ventricular function. Three-dimensional (3D) echocardiography provides valuable information regarding cardiac morphology.

#### M-MODE ECHOCARDIOGRAPHY

M-mode echocardiography displays a 1-dimensional slice of cardiac structure varying over time (Fig. 423-14). It is used mostly for the measurement of cardiac dimensions (wall thickness and chamber size) and cardiac function (fractional shortening, wall thickening). M-mode echocardiography is also useful for assessing the motion of intracardiac structures (opening and closing of valves, movement of free walls and septa) and the anatomy of valves (Fig. 423-15). The most frequently used index of cardiac function in children is percent fractional shortening (%FS), which is calculated as \((\frac{\text{LVES} - \text{LVED}}{\text{LVED}})\times 100\), where LVED is left ventricular (LV) dimension at end-diastole and LVES is

Figure 423-14 M-mode echocardiogram. A, Diagram of a sagittal section of a heart showing the structures traversed by the echo beam as it is moved superiorly to positions (1), (2), and (3). AMC, anterior mitral cusp; APM, anterior papillary muscle; Dec. aorta, descending aorta; LA, left atrium; LV, left ventricle; PMC, posterior mitral cusp; PPM, posterior papillary muscle; RV, right ventricle. B, Echocardiogram from transducer position (1); this view is the best one for measuring cardiac dimensions and fractional shortening. Fractional shortening is calculated as \((\frac{\text{LVED} - \text{LVES}}{\text{LVED}})\times 100\). CW, chest wall; Ds, LV dimension in systole; LVED, LV dimension at end-diastole (Dd); RVED, RV dimension at end-diastole.

Figure 423-15 M-mode echocardiograms. The small figure at the top of each panel shows the 2D parasternal short axis echo image from which the M-modes are derived. The cursor can be seen midway through the image, indicating the one-dimensional line through which the M-mode is being sampled. A, M-mode echocardiogram of a normal mitral valve. Arrow shows the opening of the anterior leaflet in early diastole (see ECG tracing above for reference). B, M-mode echocardiogram of a normal aortic valve. The opening and closing of the aortic leaflets in systole are outlined by the 2 arrows. Ao, aorta; IVS, interventricular septum; LV, left ventricle; RV, right ventricle.
LV dimension at end-systole. Normal fractional shortening is approximately 28-40%. Other M-mode indices of cardiac function include the mean velocity of fiber shortening (mean $V_{cf}$), systolic time intervals (LVPEP = LV preejection period, LVET = LV ejection time), and isovolumic contraction time. More sophisticated indices of cardiac function can be derived noninvasively with the assistance of echocardiography (pressure-volume relationship, end-systolic wall stress-strain relationship).

**TWO-DIMENSIONAL ECHOCARDIOGRAPHY**

Two-dimensional echocardiography provides a real-time image of cardiac structures. With 2D echocardiography, the contracting heart is imaged in real time using several standard views, including parasternal long axis (Fig. 423-16), parasternal short axis (Fig. 423-17), apical four chamber (Fig. 423-18), subcostal (Fig. 423-19), and suprasternal (Fig. 423-20) windows, each of which emphasizes specific structures. Two-dimensional echocardiography has replaced cardiac angiography for the preoperative diagnosis of most, but not all congenital heart lesions. When information from the cardiac examination or other studies is not consistent with the echocardiogram (e.g., the size of a left-to-right shunt), cardiac catheterization remains an important tool to confirm the anatomic diagnosis and evaluate the degree of physiologic derangement.

**DOPPLER ECHOCARDIOGRAPHY**

Doppler echocardiography displays blood flow in cardiac chambers and vascular channels based on the change in frequency imparted to
a sound wave by the movement of erythrocytes. In pulsed Doppler and continuous wave Doppler, the speed and direction of blood flow in the line of the echo beam change the transducer’s reference frequency. This frequency change can be translated into volumetric flow (L/min) data for estimating systemic or pulmonary blood flow and into pressure (mm Hg) data for estimating gradients across the semilunar or atrioventricular valves or across septal defects or vascular communications such as shunts. Color Doppler permits highly accurate assessment of the presence and direction of intracardiac shunts and allows identification of small or multiple left-to-right or right-to-left shunts (Fig. 423-21). The severity of valvular insufficiency can be evaluated with both pulsed and color Doppler (Fig. 423-22). Alterations in venous Doppler flow patterns can be used to detect abnormalities of systemic and pulmonary veins and alterations of atrioventricular valve Doppler flow patterns can be used to assess ventricular diastolic functional abnormalities.

M-mode, 2D, and Doppler echocardiographic methods of assessing LV systolic and diastolic function (e.g., end-systolic wall stress, dobutamine stress echocardiography, and Doppler tissue imaging) have proved useful in the serial assessment of patients at risk for the development of both systolic and diastolic ventricular dysfunction and ventricular dyssynchrony (where the coordination of left and right ventricular contraction is abnormal). Such patients include those with cardiomyopathies, those receiving anthracycline drugs for cancer chemotherapy, those at risk for iron overload, and those being monitored for rejection or coronary artery disease after heart transplantation.
The dependent diabetics, patients with exposure to teratogenic drugs are at higher risk of having a child with cardiac disease (insulin-dependent diabetics, patients with exposure to teratogenic drugs). A screening approach for detecting gross abnormalities in cardiac structure on routine obstetric ultrasonography or may refer the patient because of unexplained hydrops fetalis, a family history of congenital heart disease, or a maternal condition associated with fetal cardiac pathology such as gestational diabetes. Fetal echocardiography is capable of diagnosing most significant congenital heart lesions as early as 17-19 wk of gestation; accuracy at this early stage is limited and families should understand that these studies cannot totally eliminate the possibility of congenital heart disease. Serial fetal echocardiograms have also demonstrated the importance of flow disturbance in the pathogenesis of congenital heart disease; such studies can show the intratertiary progression of a moderate lesion, such as aortic stenosis, into a more severe lesion, such as hypoplastic left heart syndrome. M-mode echocardiography can diagnose rhythm disturbances in the fetus and can determine the success of antiarrhythmic therapy administered to the mother. A screening fetal echocardiogram is recommended for women with a previous child or 1st-degree relative with congenital heart disease, for those who are at higher risk of having a child with cardiac disease (insulin-dependent diabetics, patients with exposure to teratogenic drugs during early pregnancy), and in any fetus in which a chromosomal abnormality is suspected or confirmed.

Early detection provides the opportunity to counsel and educate the parents about the severity of the cardiac lesion and potential therapeutic or palliative care options. Referral to a high-risk perinatal service is then performed, for further ultrasound screening for associated anomalies of other organs and potential amniocentesis for karyotyping. For those fetuses with ductal dependent lesions, delivery can be planned at a tertiary care center, avoiding the requirement for postnatal transport of an unstable infant. For those fetuses with complex congenital heart disease at high risk for complications immediately at birth (e.g., hypoplastic left heart syndrome with intact atrial septum), delivery can be arranged with an operating room and surgeon standing by.

Bibliography is available at Expert Consult.

### 423.5 Exercise Testing

**Daniel Bernstein**

The normal cardiorespiratory system adapts to the extensive demands of exercise with a several-fold increase in oxygen consumption and cardiac output. Because of the large reserve capacity for exercise, significant abnormalities in cardiovascular performance may be present without symptoms at rest or during ordinary activities. When patients are evaluated in a resting state, significant abnormalities in cardiac function may not be appreciated, or if detected, their implications for quality of life may not be recognized. Permission for children with cardiovascular disease to participate in various forms of physical activity is frequently based on totally subjective criteria. As the importance of aerobic exercise is increasingly recognized, even for children with complex congenital heart lesions, exercise testing can provide a quantitative evaluation of the child’s ability to safely participate in both competitive and noncompetitive sports. Exercise testing can also play an important role in evaluating symptoms and quantitating the severity of cardiac abnormalities.

In older children, exercise studies are generally performed on a graded treadmill apparatus with timed intervals of increasing grade...
Bibliography
and speed. In younger children, exercise studies are often performed on a bicycle ergometer. Many laboratories have the capacity to measure both cardiac and pulmonary function noninvasively during exercise. This allows measurement of both resting and maximal oxygen consumption (VO2max) and the point at which anaerobic threshold is reached, important indicators of cardiovascular fitness.

As a child grows, the capacity for work is enhanced with increased body size and skeletal muscle mass. All indices of cardiopulmonary function do not increase in a uniform manner. A major response to exercise is an increase in cardiac output, principally achieved through an increase in heart rate, but stroke volume, systemic venous return, and pulse pressure are also increased. Systemic vascular resistance is greatly decreased as the blood vessels in working muscle dilate in response to increasing metabolic demands. As the child becomes older and larger, the response of the heart rate to exercise remains prominent, but cardiac output increases because of growing cardiac volume capacity and, hence, stroke volume. Responses to dynamic exercise are not dependent solely on age. For any given body surface area, boys have a larger stroke volume than size-matched girls. This increase is also mediated by posture. Augmentation of stroke volume with upright, dynamic exercise is facilitated by the pumping action of working muscles, which overcomes the static effect of gravity and increases systemic venous return.

Dynamic exercise testing defines not only endurance and exercise capacity but also the effect of such exercise on myocardial blood flow and cardiac rhythm. Significant ST segment depression reflects abnormalities in myocardial perfusion, for example, the subendocardial ischemia that commonly occurs during exercise in children with hypertrophied left ventricles. The exercise ECG is considered abnormal if the ST segment depression is >2 mm and extends for at least 0.06 sec after the J point (onset of the ST segment) in conjunction with a horizontal-, upward-, or downward-sloping ST segment. Provocation of rhythm disturbances during an exercise study is an important method of evaluating selected patients with known or suspected rhythm disorders. The effect of pharmacologic management can also be tested in this manner.

Bibliography is available at Expert Consult.

423.6 MRI, MRA, CT, and Radionuclide Studies

Daniel Bernstein

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are extremely helpful in the diagnosis and management of patients with congenital heart disease. These techniques produce tomographic images of the heart in any projection (Fig. 423-25), with excellent contrast resolution of fat, myocardium, and lung, as well as moving blood from blood vessel walls. MRI is useful in evaluating areas that are less well visualized by echocardiography, such as distal branch pulmonary artery anatomy and anomalies in systemic and pulmonary venous return.

MRA allows the acquisition of images in several tomographic planes. Within each plane, images are obtained at different phases of the cardiac cycle. Thus, when displayed in a dynamic "cine" format, changes in wall thickening, chamber volume, and valve function can be displayed and analyzed. Blood flow velocity and blood flow volume can be calculated. MRA is an excellent technique for following patients serially after repair of complex congenital heart disease, such as tetralogy of Fallot. In these patients, MRA can be used to assess right ventricular volume and mass as well as quantify the amount of regurgitation through either the pulmonary or tricuspid valve. Other MRI techniques, such as myocardial delayed enhancement, can be used to quantify areas of myocardial scar in patients with cardiomyopathy or in patients after congenital heart disease repair, especially tetralogy of Fallot. Magnetic resonance spectroscopy, predominantly a research tool at present, provides a means of demonstrating relative concentrations of high-energy metabolites (adenosine triphosphate, adenosine diphosphate, inorganic phosphate, and phosphocreatine) within regions of the working myocardium.

Computer processing of MRA images allows the noninvasive visualization of the cardiovascular system from inside of the heart or vessels, a technique known as fly-through imaging. These images allow the cardiologist to image the interiors of various cardiovascular structures (Fig. 423-26). These imaging techniques are especially helpful in imaging complex peripheral arterial stenoses, especially after balloon angioplasty.

CT scanning can now be used to perform rapid, respiration-gated cardiac imaging in children with resolutions down to 0.5 mm. Three-dimensional reconstruction of CT images (Fig. 423-27) are especially useful in evaluating branch pulmonary arteries, anomalies in systemic and pulmonary venous return, and great vessel anomalies such as coarctation of the aorta.

Radionuclide angiography may be used to detect and quantify shunts and to analyze the distribution of blood flow to each lung. This technique is particularly useful in quantifying the volume of blood flow distribution between the 2 lungs in patients with abnormalities of the pulmonary vascular tree or after a shunt operation (Blalock-Taussig or Glenn), or to quantify the success of balloon angioplasty and intra-vascular stenting procedures. Gated blood pool scanning can be used to calculate hemodynamic measurements, quantify valvular regurgitation, and detect regional wall motion abnormalities. Thallium imaging can be performed to evaluate cardiac muscle perfusion. These methods can be used at the bedside of seriously ill children and can be performed serially, with minimal discomfort and low radiation exposure.

Bibliography is available at Expert Consult.
Bibliography


Bibliography
Figure 423-27 Three-dimensional reconstruction of electron-beam CT images from a neonate with severe coarctation of the aorta. The patent ductus arteriosus can be seen toward the left leading from the main pulmonary artery to the descending aorta. The tortuous and narrow coarctated segment is just to the right of the ductus. The transverse aorta is hypoplastic as well. AAo, ascending aorta; DAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RAA, right atrial appendage; RPA, right pulmonary artery. (Image courtesy of Dr. Paul Pitlick, Stanford University, Stanford, CA.)

423.7 Diagnostic and Interventional Cardiac Catheterization

Daniel Bernstein

The catheterization laboratory has become the site of high-technology interventional procedures, allowing for the nonsurgical repair or palliation of heart defects that once required open heart surgery. Some centers have developed hybrid catheterization laboratories, combining standard fluoroscopic imaging with an operating suite, allowing combined approaches to treat complex congenital heart lesions.

DIAGNOSTIC CARDIAC CATHETERIZATION

Diagnostic catheterization is still performed: (1) to assist in the initial diagnosis of some complex congenital heart lesions (e.g., tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries, pulmonary atresia with intact ventricular septum and coronary sinusoids, hypoplastic left-heart syndrome with mitral stenosis); (2) in cases in which other imaging studies are equivocal; (3) in patients for whom hemodynamic assessment is critical (to determine the size of a left-to-right shunt in borderline cases, or to determine the presence or absence of pulmonary vascular disease in an older patient with a left-to-right shunt); (4) between stages of repair of complex congenital heart disease (e.g., hypoplastic left- or right-heart syndromes); (5) for myocardial biopsy in the diagnosis of cardiomyopathy or in
Cineangiograms are exposed at rates ranging from 15-60 frames/sec. The amount of contrast medium is injected with a power injector, and the catheter as it passes through the various heart chambers. After the injection of contrast material during selective angiocardiography, the injection of contrast material and measurement of pulmonary artery and pulmonary capillary wedge pressure. crowding of the heart can be catheterized by passing the catheter retrograde via the left atrium and left ventricle. If the foramen is closed, the left side of the heart can be catheterized by passing the catheter retrograde via a percutaneous entry site in the femoral or jugular vein. The catheter is passed into the heart under fluoroscopic guidance and angiography is greatest in critically ill infants; they must be studied in a thermally neutral environment and treated quickly for hypothermia, hypoglycemia, acidosis, or excessive blood loss.

Catheterization may be limited to the right-sided cardiac structures, the left-sided structures, or both the right and left sides of the heart. The catheter is passed into the heart through a femoral or jugular vein. In infants and a number of older children, the left side of the heart can be accessed by passing the catheter across a patent foramen ovale to the left atrium and left ventricle. If the foramen is closed, the left side of the heart can be catheterized by passing the catheter retrograde via a percutaneous entry site in the femoral artery, or if necessary, via a transatrial septal puncture. The catheter can be manipulated through normal intracardiac defects (ASDs, VSDs). Blood samples are obtained for measuring oxygen saturation and calculating shunt volumes, pressures are measured for calculating gradients and valve areas, and radiopaque contrast is injected to delineate cardiac and vascular structures. A catheter with a thermosensor tip can be used to measure cardiac output by thermodilution. Specialized catheters can be used to measure more sophisticated indices of cardiac function: Those with pressure-transducer tips can be utilized to measure the first derivative of LV pressure (dP/dt); and conductance catheters can be used to generate pressure-volume loops, from which indices of both contractility (end-systolic elastance) and relaxation can be derived. Complete hemodynamics can be calculated, including cardiac output, intracardiac left-to-right and right-to-left shunts, and systemic and pulmonary vascular resistances. Figure 423-28 depicts normal circulatory dynamics.

**THERMODILUTION MEASUREMENT OF CARDIAC OUTPUT**

The thermodilution method for measuring cardiac output is performed with a flow-directed, thermistor-tipped, pulmonary artery (Swan-Ganz) catheter. A known change in the heat content of the blood is induced at one point in the circulation (usually the right atrium or inferior vena cava) by injecting room temperature saline, and the resultant change in temperature is detected at a point downstream (usually the pulmonary artery). This method is used to measure cardiac output in the catheterization laboratory in patients without shunts. Monitoring cardiac output by the thermodilution method can occasionally be useful in managing critically ill infants and children in an intensive care setting after cardiac surgery or in the presence of shock. In this case, a triple-lumen catheter is used for both cardiac output determination and measurement of pulmonary artery and pulmonary capillary wedge pressure.

**ANGIOCARDIOGRAPHY**

The major blood vessels and individual cardiac chambers may be visualized by selective angiography, the injection of contrast material into specific chambers or great vessels. This method allows identification of structural abnormalities without interference from the superimposed shadows of normal chambers. Fluoroscopy is used to visualize the catheter as it passes through the various heart chambers. After the cardiac catheter is properly placed in the chamber to be studied, a small amount of contrast medium is injected with a power injector, and cineangiograms are exposed at rates ranging from 15-60 frames/sec. Screening for cardiac rejection after cardiac transplantation; and (6) for electrophysiologic study in the evaluation of cardiac arrhythmias (see Chapter 435).

Cardiac catheterization should be performed with the patient in as close to a basal state as possible. Conscious sedation is routine; if a deeper level of general anesthesia is required, careful choice of an anesthetic agent is warranted to avoid depression of cardiovascular function and subsequent distortion of the calculations of cardiac output, pulmonary and systemic vascular resistance, and shunt ratios.

Cardiac catheterization in critically ill infants with congenital heart disease should be performed in a center where a pediatric cardiovascular surgical team is available. In the event that an operation is required immediately afterward. The complication rate of cardiac catheterization and angiography is greatest in critically ill infants; they must be studied in a thermally neutral environment and treated quickly for hypothermia, hypoglycemia, acidosis, or excessive blood loss.

Figure 423-28: Diagram of normal circulatory dynamics with pressure readings, oxygen content, and percent saturation. B.S.A., body surface area. (Modified from Nadas AS, Fyler DC: Pediatric cardiology, ed 3, Philadelphia, 1972, WB Saunders.)

Modern catheterization labs use digital imaging technology, allowing for a significant reduction in radiation exposure. Biplane cineangiography allows detailed evaluation of specific cardiac chambers and blood vessels in 2 planes simultaneously with the injection of a single bolus of contrast material. This technique is standard in pediatric cardiac catheterization laboratories and allows one to minimize the volume of contrast material used, which is safer for the patient. Various angled views (e.g., left anterior oblique, cranial angulation) are used to display specific anatomic features best in individual lesions.

Rapid injection of contrast medium under pressure into the circulation is not without risk, and each injection should be carefully planned. Contrast agents consist of hypertonic solutions, with some containing organic iodides, which can cause complications, including nausea, a generalized burning sensation, central nervous system symptoms, renal insufficiency, and allergic reactions. Intramyocardial injection is generally avoided by careful placement of the catheter before injection. Hypertonicity of the contrast medium may result in transient myocardial depression and a drop in blood pressure, followed soon afterward by tachycardia, an increase in cardiac output, and a shift of interstitial fluid into the circulation. This shift can transiently increase the symptoms of heart failure in critically ill patients.

**INTERVENTIONAL CARDIAC CATHETERIZATION**

Catheter treatment is the standard of practice for most cases of isolated pulmonary or aortic valve stenosis (see Fig. 421-4) as well as for re-coarctation of the aorta. A special catheter with a sausage-shaped balloon at the distal end is passed through the obstructed valve. Rapid filling of the balloon with a mixture of contrast material and saline solution results in tearing of the stenotic valve tissue, usually at the site of inappropriately fused raphe. Valvular pulmonary stenosis can be treated successfully by balloon angioplasty; in most patients, angioplasty has replaced surgical repair as the initial procedure of choice.
The clinical results of this procedure are similar to those obtained by open heart surgery, but without the need for sternotomy or prolonged hospitalization. Balloon valvuloplasty for aortic stenosis has also yielded excellent results, although, as with surgery, aortic stenosis often recurs as the child grows and multiple procedures may thus be required. One complication of both valvuloplasty and surgery is the creation of valvular insufficiency. This complication has more serious implications when it occurs on the aortic vs the pulmonary side of the circulation because regurgitation is less-well tolerated at systemic arterial pressures. Balloon angioplasty is the procedure of choice for patients with restenosis of coarctation of the aorta after earlier surgery. It is controversial whether angioplasty is the best procedure for native (unoperated) coarctation of the aorta because of reports of later aneurysm formation and most centers still refer primary coarctation in infants and young children for surgical repair. However, in older patients with previously undiagnosed coarctation, especially those with decreased LV function, primary angioplasty with possible stent placement may be considered. Other applications of the balloon angioplasty technique include amelioration of mitral stenosis, dilation of surgical conduits (Mustard or Senning atrial baffles), relief of branch pulmonary artery narrowing, dilation of systemic or pulmonary venous obstructions, and the long-used balloon atrial septostomy (Rashkind procedure) for transposition of the great arteries (see Chapter 431.2).

Interventional catheterization techniques are being adapted for use in the fetus with lesions such as aortic stenosis in an attempt to prevent their progression to more complex lesions such as hypoplastic left heart syndrome. In these procedures, after administration of appropriate anesthesia, a needle is passed through the maternal abdominal wall, the uterine wall, and the fetal chest wall and directly into the fetal left ventricle (see Fig. 425-13). A coronary angioplasty balloon catheter is passed through the needle and across the stenotic aortic valve, which is then dilated. With the restoration of normal LV blood flow, it is to be hoped that normal LV growth potential is restored. Midterm results with this technique in a growing number of patients show mixed results with good ventricular growth leading to a 2-ventricle circulation in approximately 25% of patients.

In patients with branch pulmonary artery stenoses, the previously mixed results with balloon angioplasty alone have been enhanced with the use of intravascular stents (Fig. 423-29) delivered over a balloon catheter and expanded within the vessel lumen. Once placed, they can often be dilated to successively greater sizes as the patient grows, although their use in younger infants and children is limited by the extent to which they can be further expanded. Research into biodissolvable stents may solve this problem in the future. Stents are also being used in adolescents and young adults with coarctation of the aorta.

Closure of a small PDA is routinely achieved with catheter-delivered coils (see Fig. 420-11), whereas a larger PDA can be closed with a variety of sandwich-type devices. Closure of anomalous vascular connections (coronary fistulas, venovenous collaterals in cyanotic heart lesions) can also be achieved using coils. Secundum ASDs are now routinely closed with a double-disc occluder device (see Fig. 420-3). Versions of these devices are currently in clinical trials for closure of surgically hard-to-reach muscular VSDs and even for the more common perimembranous VSD. Catheter-delivered devices may also be used as an adjunct to complex surgical repairs (dilation or stenting of branch pulmonary artery or pulmonary vein stenosis or closure of a difficult to reach muscular VSD). High-risk patients undergoing the Fontan operation (see Chapter 430.4) often have a small fenestration created between the right and left sides of the circulation to serve as a “popoff valve” for high right-sided pressure in the early surgical period. Patients with these “fenestrated Fontans” are usually candidates for subsequent closure of the fenestration with a catheter-delivered device.

Bibliography is available at Expert Consult.
Bibliography
Prevalence

Congenital heart disease occurs in approximately 0.8% of live births. The incidence is higher in stillborns (3-4%), spontaneous abortuses (10-25%), and premature infants (approximately 2% excluding patent ductus arteriosus [PDA]). This overall incidence does not include mitral valve prolapse, PDA of preterm infants, and bicuspid aortic valves (present in 1-2% of adults). Congenital cardiac defects have a wide spectrum of severity in infants: approximately 2-3 in 1,000 newborn infants will be symptomatic with heart disease in the 1st yr of life. The diagnosis is established by 1 wk of age in 40-50% of patients with congenital heart disease and by 1 mo of age in 50-60% of patients. With advances in both palliative and corrective surgery, the number of children with congenital heart disease surviving to adulthood has increased dramatically. Despite these advances, congenital heart disease remains the leading cause of death in children with congenital malformations. Table 424-1 summarizes the relative frequency of the most common congenital cardiac lesions.

Most congenital defects are well tolerated in the fetus because of the parallel nature of the fetal circulation. Even the most severe cardiac defects (e.g., hypoplastic left-heart syndrome) can usually be well compensated for by the fetal circulation. In this example, the entire fetal
Relative Frequency of Major Congenital Heart Lesions

<table>
<thead>
<tr>
<th>LESION</th>
<th>% OF ALL LESIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect</td>
<td>35-30</td>
</tr>
<tr>
<td>Atrial septal defect (secundum)</td>
<td>6-8</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>6-8</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>5-7</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>5-7</td>
</tr>
<tr>
<td>Pulmonary valve stenosis</td>
<td>5-7</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>4-7</td>
</tr>
<tr>
<td>D-Transposition of great arteries</td>
<td>3-5</td>
</tr>
<tr>
<td>Hypoplastic left ventricle</td>
<td>1-3</td>
</tr>
<tr>
<td>Hypoplastic right ventricle</td>
<td>1-3</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>1-2</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return</td>
<td>1-2</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>1-2</td>
</tr>
<tr>
<td>Single ventricle</td>
<td>1-2</td>
</tr>
<tr>
<td>Double-outlet right ventricle</td>
<td>1-2</td>
</tr>
<tr>
<td>Others</td>
<td>5-10</td>
</tr>
</tbody>
</table>

*Excluding patent ductus arteriosus in preterm neonates, bicuspid aortic valve, physiologic peripheral pulmonic stenosis, and mitral valve prolapse.

cardiac output would be ejected by the right ventricle via the duc tus arteriosus into both the descending and ascending aorta (the latter filling in a retrograde fashion), so that fetal organ blood flow would be minimally perturbed. Because the placenta provides for gas exchange and the normal fetal circulation has mixing between more highly and more poorly oxygenated blood, fetal organ oxygen delivery is also not dramatically affected. It is only after birth when the fetal pathways (ductus arteriosus and foramen ovale) begin to close that the full hemodynamic impact of an anatomic abnormality becomes apparent. One notable exception is the case of severe regurgitant lesions, most commonly of the tricuspid valve. In these lesions (e.g., Ebstein anomaly or severe right ventricular outflow obstruction [see Chapter 430.7]), the parallel fetal circulation cannot compensate for the volume load imposed on the right side of the heart. In utero heart failure, often with fetal pleural and pericardial effusions, and generalized ascites (nonimmune hydrops fetalis) may occur.

Although the most significant transitions in circulation occur in the immediate perinatal period, the circulation continues to undergo changes after birth, and these later changes may also have a hemodynamic impact on cardiac lesions and their apparent incidence. As pulmonary vascular resistance falls in the 1st several weeks of life, left-to-right shunting through intracardiac defects increases and symptoms become more apparent. Thus, in patients with a ventricular septal defect (VSD), heart failure is often first noticed between 1 and 3 mo of age (see Chapter 426.6). The severity of various defects can also change dramatically with growth; some VSDs may become smaller and even close as the child ages. Alternatively, stenosis of the aortic or pulmonary valve, which may be only moderate in the newborn period, may become worse if valve orifice growth does not keep pace with patient growth (see Chapter 427.5). The physician should always be alert for associated congenital malformations, which can adversely affect the patient’s prognosis (see Table 422-2 in Chapter 422).

ETIOLOGY
The cause of most congenital heart defects is still unknown. Many cases of congenital heart disease are multifactorial and result from a combination of genetic predisposition and an as-yet-to-be-determined environmental stimulus. A small percentage of congenital heart lesions are related to known chromosomal abnormalities, in particular, trisomy 21, 13, and 18 and Turner syndrome; heart disease is found in more than 90% of patients with trisomy 18, 50% of patients with trisomy 21, and 40% of those with Turner syndrome. Other genetic factors may have a role in congenital heart disease; e.g., certain types of VSDs (supracristal) are more common in Asian children. The risk of occurrence of congenital heart disease increases if a 1st-degree relative (parent or sibling) is affected.

A growing list of congenital heart lesions has been associated with specific chromosomal abnormalities, and several have even been linked to specific gene defects. Fluorescent in situ hybridization analysis allows clinicians rapid screening of suspected cases once a specific chromosomal abnormality has been identified, although clinical laboratory tests for specific gene defects are still uncommon. In addition, microarray genomic hybridization has identified previously unknown copy number variations (microdeletions or microduplications) in many patients with congenital heart disease and suspicion of a congenital anomaly syndrome. These variants are submicroscopic and thus not visible on routine chromosome analysis.

A well-characterized genetic cause of congenital heart disease is the deletion of a large region (1.5-3 Mb) of chromosome 22q11.2, known as the DiGeorge critical region. At least 30 genes have been mapped to the deleted region; Tbx1, a transcription factor involved in early outflow tract development is one gene that has been implicated as a possible cause of DiGeorge syndrome. The estimated prevalence of 22q11.2 deletions is 1/4,000 live births. Cardiac lesions associated with 22q11.2 deletions are most often seen in association with either the DiGeorge syndrome or the Shprintzen (velocardiofacial) syndrome. The acronym CATCH 22 has been used to summarize the major components of these syndromes (cardiac defects, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia). The specific cardiac anomalies are conotruncal defects (tetralogy of Fallot, truncus arteriosus, double-outlet right ventricle, subarterial VSD) and branchial arch defects (coarctation of the aorta, interrupted aortic arch, right aortic arch). Congenital airway abnormalities such as tracheomalacia and bronchomalacia are sometimes present. Although the risk of recurrence is extremely low in the absence of a parental 22q11.2 deletion, it is 50% if 1 parent carries the deletion. More than 90% of patients with the clinical features of DiGeorge syndrome have a deletion at 22q11.2. A second genetic locus on the short arm of chromosome 10 (10p13p14) has also been identified, the deletion of which shares some, but not all, phenotypic characteristics with the 22q11.2 deletion; patients with del(10p) have an increased incidence of sensorineural hearing loss.

Other structural heart lesions that have been associated with specific chromosomal abnormalities include familial secundum atrial septal defect associated with heart block (the transcription factor Nkx2.5 on chromosome 5q35), familial atrial septal defect without heart block (the transcription factor GATA4), Alagille syndrome (jagged1 on chromosome 20p12), and Williams syndrome (elastin on chromosome 7q11). Of interest, patients with VSDs and atroventricular septal defects have been found to have multiple Nkx2.5 mutations in cells isolated from diseased heart tissues, but not from normal heart tissues or from circulating lymphocytes, indicating a potential role for somatic mutations leading to mosaicism in the pathogenesis of congenital heart defects. Tables 424-2 and 424-3 are a compilation of known genetic causes of congenital heart disease.

The most progress in identifying the genetic origin of cardiovascular disease has been made in the genetic cardiomyopathies, and in particular, hypertrophic cardiomyopathy. Mutations in several genes have been implicated, most of which encode protein components of the cardiac sarcomere, either components of the thick or thin fibers or associated regulatory subunits, although mutations in mitochondrial genes are increasingly recognized and play a larger role in those presenting with hypertrophic cardiomyopathy as young infants than in older children and adults. Mutations of the cardiac β-myosin heavy-chain gene (chromosome 14q11) and the myosin-binding protein C gene (chromosome 11q11) are the most common (see Table 424-4), with less-common mutations including the cardiac tropinon T and I genes, α-tropomyosin, regulatory and essential myosin light chains, titin, and the α-myosin heavy chain. More than 200 mutations have
Table 424-2  Genetics of Congenital Heart Disease: Defects Associated with Syndromes

<table>
<thead>
<tr>
<th>CARDIOVASCULAR DISEASE</th>
<th>CHROMOSOMAL LOCATION</th>
<th>GENE(S) IMPLICATED*</th>
<th>COMMON CARDIAC DEFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiGeorge syndrome, velocardiofacial syndrome</td>
<td>22q11.2, 11p13p14</td>
<td>TBX1</td>
<td>TOF, IAA, TA, VSD</td>
</tr>
<tr>
<td>Familial ASD with heart block</td>
<td>5q35</td>
<td>NXX2.5</td>
<td>ASD, heart block</td>
</tr>
<tr>
<td>Familial ASD without heart block</td>
<td>8p22-23</td>
<td>GATA4</td>
<td>ASD</td>
</tr>
<tr>
<td>Alagille syndrome (bile duct hypoplasia, right-sided cardiac lesions)</td>
<td>20p12, 1p12</td>
<td>JAGGED1, NOTCH2</td>
<td>Peripheral pulmonary hypoplasia, PS, TOF</td>
</tr>
<tr>
<td>Holt-Oram syndrome (limb defects, ASD)</td>
<td>12q24</td>
<td>TBX5</td>
<td>ASD, VSD, PDA</td>
</tr>
<tr>
<td>Trisomy 21 (Down syndrome)</td>
<td>21q22</td>
<td>Not known</td>
<td>AVSD</td>
</tr>
<tr>
<td>Isolated familial AV septal defect (without trisomy 21)</td>
<td>1p31-p21, 3p25</td>
<td>CRELD1</td>
<td>AVSD</td>
</tr>
<tr>
<td>Familial TAPVR</td>
<td>4p13-q12</td>
<td>Not known</td>
<td>TAPVR</td>
</tr>
<tr>
<td>Noonan syndrome (PS, ASD, hypertrophic cardiomyopathy)</td>
<td>12q24, 12p1.21, 2p212, 3p25.2, 7q34, 15q22.31, 11p15.5, 1p13.2, 10q25.2, 11q23.3, 17q11.2</td>
<td>PTPN11, KRAS, SOS1, RAF1, BRAF, MEK1, HRAS, NRAS, SHOC2, CBL, NF1</td>
<td>PS, ASD, VSD, PDA, cardiomyopathy</td>
</tr>
<tr>
<td>Ellis–van Creveld syndrome (polydactyly, ASD)</td>
<td>4p16</td>
<td>EVC, EVC2</td>
<td>ASD, common atrium</td>
</tr>
<tr>
<td>Char syndrome (craniofacial, limb defects, PDA)</td>
<td>6p12-21.1</td>
<td>TFAP2B</td>
<td>PDA</td>
</tr>
<tr>
<td>Williams-Beuren syndrome (supravalvar AS, branch PS, hypercalcemia)</td>
<td>7q11.23</td>
<td>ELN (Elastin)</td>
<td>Supravalvar AS, peripheral PS</td>
</tr>
<tr>
<td>Marfan syndrome (connective tissue weakness, aortic root dilation)</td>
<td>15q21</td>
<td>Fibrillin</td>
<td>Aortic aneurysm, mitral valve disease</td>
</tr>
<tr>
<td>Familial laterality abnormalities</td>
<td>Xq24-2q7, 1q42, 9p13-21</td>
<td>ZIC3, DNAJ1</td>
<td>Situs inversus, complex congenital heart disease</td>
</tr>
<tr>
<td>Turner</td>
<td>X</td>
<td>Not known</td>
<td>Coarctation of the aorta, Aortic stenosis</td>
</tr>
<tr>
<td>Trisomy 13 (Patau syndrome)</td>
<td>13</td>
<td>Not known</td>
<td>ASD, VSD, PDA, Valve abnormalities</td>
</tr>
<tr>
<td>Trisomy 18 (Edwards syndrome)</td>
<td>18</td>
<td>Not known</td>
<td>ASD, VSD, PDA, Valve abnormalities</td>
</tr>
<tr>
<td>Cri du chat</td>
<td>5p15.2</td>
<td>CTNND2</td>
<td>ASD, VSD, PDA, TOF</td>
</tr>
<tr>
<td>Cat eye</td>
<td>22q11</td>
<td>Not known</td>
<td>TAPVR, TOF</td>
</tr>
<tr>
<td>Jacobsen</td>
<td>11q23</td>
<td>JAM-3</td>
<td>HLHS</td>
</tr>
<tr>
<td>Costello</td>
<td>11p15.5</td>
<td>HRAS</td>
<td>PS, hypertrophic cardiomyopathy, arrhythmias</td>
</tr>
<tr>
<td>CHARGE</td>
<td>8p12, 7q21.11</td>
<td>CHD7, SEMA3E</td>
<td>ASD, VSD, TOF</td>
</tr>
<tr>
<td>Kabuki syndrome</td>
<td>12q13.12</td>
<td>MLL2</td>
<td>ASD, VSD, TOF, coarctation, TGA</td>
</tr>
<tr>
<td>Carney syndrome</td>
<td>2p16</td>
<td>PRKARTA</td>
<td>Atrial and ventricular myxomas</td>
</tr>
</tbody>
</table>

AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; AVSD, atrioventricular septal defect; HLHS, hypoplastic left-heart syndrome; IAA, interrupted aortic arch; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*In many cases, mutation of a single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

been identified in these genes, and some patients may carry mutations in more than 1 gene. Routine clinical laboratory tests are now available for most of these mutations.

Progress has also been made in identifying the genetic basis of dilated cardiomyopathy, which is familial in 20-50% of cases. Autosomal dominant inheritance is most commonly encountered and, similar to hypertrophic cardiomyopathy, multiple genes have been identified (see Table 424-2). X-linked inheritance accounts for 5-10% of cases of familial dilated cardiomyopathy. Mutations in the dystrophin gene (chromosome Xp21) are the most common in this group. Mutations in the gene encoding fagazzin are associated with Barth syndrome and some cases of isolated non-compaction of the
left ventricle. Autosomal recessive inheritance is associated with a mutation in cardiac troponin I. Mitochondrial myopathies may be caused by mutations of enzymes of the electron transport chain or enzymes of fatty acid oxidation encoded by mitochondrial DNA (which is inherited solely from the mother). Table 424-2 is a compilation of the most common genetic causes of congenital heart disease.

The genetic basis of heritable arrhythmias, most notably the long QT syndromes, has been linked to mutations of genes coding for subunits of cardiac potassium and sodium channels (see Table 424-2). Other heritable arrhythmias include arrhythmogenic right ventricular dysplasia, familial atrial fibrillation, familial complete heart block, and Brugada syndrome. Table 424-3 is a compilation of the most common genetic causes of arrhythmias.

Of all cases of congenital heart disease, 2-4% are associated with autosomal recessive inheritance. Mitochondrial myopathies may be caused by mutations of enzymes of the electron transport chain or enzymes of fatty acid oxidation encoded by mitochondrial DNA (which is inherited solely from the mother). Table 424-2 is a compilation of the most common genetic causes of congenital heart disease.

Table 424-3: Genetics of Isolated Congenital Heart Disease (Nonsyndromic)

<table>
<thead>
<tr>
<th>GENES ENCODING GENETIC FACTORS</th>
<th>PROTEIN ENCODED</th>
<th>CARDIAC DEFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANKRBD1</td>
<td>Ankyrin repeat domain</td>
<td>TAPVR</td>
</tr>
<tr>
<td>CITED2</td>
<td>cAMP responsive element-binding protein</td>
<td>ASD, VSD</td>
</tr>
<tr>
<td>FOG2/2PMP2</td>
<td>Friend of GATA</td>
<td>TOF</td>
</tr>
<tr>
<td>GATA6</td>
<td>GATA6 transcription factor</td>
<td>ASD, VSD, TOF, PS, AVSD, PDA</td>
</tr>
<tr>
<td>HAND2</td>
<td>Helix-loop-helix transcription factor</td>
<td>TOF</td>
</tr>
<tr>
<td>IRX4</td>
<td>Iroquois homeobox 4</td>
<td>VSD</td>
</tr>
<tr>
<td>MED13L</td>
<td>Mediator complex subunit 13-like</td>
<td>TGA</td>
</tr>
<tr>
<td>NKX2.5/NKX2.5</td>
<td>Homeobox containing transcription factor</td>
<td>ASD, VSD, TOF, HLHS, CoA, TGA, IAA</td>
</tr>
<tr>
<td>TBX20</td>
<td>T-Box 20 transcription factor</td>
<td>TGA, PS, TAPVR, HLHS, ASD, VSD</td>
</tr>
<tr>
<td>ZIC3</td>
<td>Zinc finger transcription factor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GENES ENCODING RECEPTORS AND SIGNALING MOLECULES</th>
<th>ENCODING MOLECULES</th>
<th>ENCODING SIGNALING MOLECULES</th>
<th>SIGNALING MOLECULES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACRV1/ALK2</td>
<td>BMP receptor</td>
<td>AVSD</td>
<td></td>
</tr>
<tr>
<td>ACRV2B</td>
<td>Activin receptor</td>
<td>TOF</td>
<td></td>
</tr>
<tr>
<td>ALDH1A2</td>
<td>Retinaldehyde dehydrogenase</td>
<td>TOF, TGA, AVSD, ASD, VSD, IAA, DORV</td>
<td></td>
</tr>
<tr>
<td>CFC1/CRYPTIC</td>
<td>Cryptic protein</td>
<td>ASD, AVD</td>
<td></td>
</tr>
<tr>
<td>CRELD1</td>
<td>Epidermal growth factor-related proteins</td>
<td>TOF, TGA, AVSD, ASD, VSD, IAA, DORV</td>
<td></td>
</tr>
<tr>
<td>FOXH1</td>
<td>Forkhead activin signal transducer</td>
<td>ASD, AVD, TAPVR, AVSD</td>
<td></td>
</tr>
<tr>
<td>GDF1</td>
<td>Growth differentiation factor-1</td>
<td>TGA, AVD, IAA, CoA</td>
<td></td>
</tr>
<tr>
<td>GJA1</td>
<td>Connexin 43</td>
<td>TGA, PA, TOF, DORV, TAPVR, AVSD</td>
<td></td>
</tr>
<tr>
<td>LEFTY2</td>
<td>Left-right determination factor</td>
<td>Bicuspid aortic valve, AS, CoA, HLHS</td>
<td></td>
</tr>
<tr>
<td>NODAL</td>
<td>Nodal homolog (TGF-β superfamily)</td>
<td>TAPVR</td>
<td></td>
</tr>
<tr>
<td>NOTCH1</td>
<td>NOTCH1 (Ligand of JAG1)</td>
<td>Bicuspid aortic valve, AS, CoA, HLHS</td>
<td></td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Platelet-derived growth factor receptor α</td>
<td>TAPVR</td>
<td></td>
</tr>
<tr>
<td>SMAD6</td>
<td>MAD-related protein</td>
<td>Outflow tract defects</td>
<td></td>
</tr>
<tr>
<td>TAB2</td>
<td>TGF-β activated kinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TED1</td>
<td>Teratocarcinoma-derived growth factor 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GENES ENCODING STRUCTURAL PROTEINS</th>
<th>ENCODING PROTEIN</th>
<th>ENCODING CARDIAC DEFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTC</td>
<td>α-Cardiac actin</td>
<td>ASD</td>
</tr>
<tr>
<td>MYH11</td>
<td>Myosin heavy chain 11</td>
<td>ASD, aortic aneurysm</td>
</tr>
<tr>
<td>MYH6</td>
<td>α-Myosin heavy chain</td>
<td>AS, TA, AS, TGA</td>
</tr>
<tr>
<td>MYH7</td>
<td>β-Myosin heavy chain</td>
<td>Ebstein anomaly, ASD</td>
</tr>
</tbody>
</table>

Gender differences in the occurrence of specific cardiac lesions have been identified. Transposition of the great arteries and left-sided obstructive lesions are slightly more common in boys (≈65%), whereas atrial septal defect, VSD, PDA, and pulmonic stenosis are more common in girls. No racial differences in the occurrence of congenital heart lesions as a whole have been noted; for specific lesions such as transposition of the great arteries, a higher occurrence is seen in white infants.

**GENETIC COUNSELING**

Parents who have a child with congenital heart disease require counseling regarding the probability of a cardiac malformation occurring in subsequent children (see Chapter 77). With the exception of syndromes known to be caused by mutation of a single gene, most congenital heart disease is still relegated to a multifactorial inheritance pattern, which should result in a low risk of recurrence. As more genetic etiologies are identified, however, these risks will need constant updating. The incidence of congenital heart disease in the normal population is 0.8%, and this incidence increases to 2-6% for a second pregnancy after the birth of a child with congenital heart disease or if a parent is affected. This recurrence risk is highly dependent on the type of lesion in the first child. When two 1st-degree relatives have congenital heart disease, the risk for a subsequent child may reach 20-30%. When a second child is found to have congenital heart disease, it will tend to be of a similar
class as the lesion in their 1st-degree relative (conotruncal lesions, left-sided obstructive lesions, right-sided obstructive lesions, atrioreal ventricular septation defects). The degree of severity may be variable, as is the presence of associated defects. Careful echocardiographic screening of 1st-degree relatives will often uncover mild forms of congenital heart disease that were clinically silent. For example, the incidence of bicuspid aortic valve is more than double (5% vs. 2% in the general population) in the relatives of children with left ventricular outflow obstructions (aortic stenosis, coarctation of the aorta, or hypoplastic left heart syndrome). Given the rapid advancements in the field of cardiovascular
consultation with a knowledgeable genetic counselor is the most reliable way of providing the family with up-to-date information regarding the risk of recurrence.

Fetal echocardiography improves the rate of detection of congenital heart lesions in high-risk patients (see Chapter 423). The resolution and accuracy of fetal echocardiography are excellent, but not perfect; families should be counseled that a normal fetal echocardiogram does not guarantee the absence of congenital heart disease. Congenital heart lesions may evolve in the course of the pregnancy; moderate aortic stenosis with a normal-sized left ventricle at 18 wk of gestation may evolve into aortic atresia with a hypoplastic left ventricle by 34 wk because of decreased flow through the atria, ventricle, and aorta in the latter half of gestation. This progression has prompted initial clinical trials of interventional treatment, such as fetal aortic balloon valvuloplasty, for the prevention of hypoplastic left heart syndrome (see Chapter 423.7).

The major factor in determining whether a woman with congenital heart disease, either unoperated or operated, will be able to carry a fetus to term is the mother's cardiovascular status. In the presence of a mild congenital heart defect or after successful repair of a more complex lesion, normal childbearing is likely. In a woman with palliated congenital heart disease or with poor cardiac function, however, the increased hemodynamic burden imposed by pregnancy may result in a significantly increased risk to both the mother and fetus. The incidence of spontaneous abortion in the presence of severe congenital heart disease is high, especially when the mother is cyanotic. The maternal risk in these situations is also high, and these pregnancies should be managed by an experienced perinatologist in conjunction with a cardiologist with expertise in adult congenital heart disease (see Chapter 434.1). It is important to discuss these risks, as well as various methods of birth control, with young women who have repaired or palliated congenital heart lesions. Antibiotic prophylaxis against endocarditis may also be indicated at the time of delivery.

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The increased volume of blood in the lungs decreases pulmonary compliance and increases the work of breathing. Fluid leaks into the interstitial space and alveoli and causes pulmonary edema. The infant develops the symptoms we refer to as heart failure, such as tachypnea, tachycardia, sweating, chest retractions, nasal flaring, and wheezing. For children with large left-to-right shunts, the term heart failure is a misnomer; however; total left ventricular output is not decreased but is actually several times greater than normal, although much of this volume is shunted away from the pulmonary circulation.
output is ineffective because it returns directly to the lungs. To maintain this high level of left ventricular output, heart rate and stroke volume are increased, mediated by an increase in sympathetic nervous system activity. The increase in circulating catecholamines, combined with the increased work of breathing, results in an elevation in total body oxygen consumption, often beyond the oxygen transport ability of the circulation. Sympathetic activation leads to the additional symptoms of sweating and irritability and the imbalance between oxygen supply and demand lead to failure to thrive. Remodeling of the heart occurs, with predominantly chamber dilation and a lesser degree of hypertrophy. If left untreated, pulmonary vascular resistance eventually begins to rise and, by several years of age, the shunt volume will decrease and eventually reverse to right-to-left (Eisenmenger physiology; see Chapter 433.2).

Additional lesions that impose a volume load on the heart include regurgitant lesions (see Chapter 428) and the cardiomyopathies (see Chapter 439). Regurgitation through the AV valves is most commonly encountered in patients with partial or complete AV septal defects (AV canal, endocardial cushion defects). In these lesions, the combination of a left-to-right shunt with AV valve regurgitation increases the volume load on the heart and often leads to more severe symptoms. Isolated regurgitation through the tricuspid valve is seen in mild, moderate and severe forms of Ebstein anomaly (see Chapter 430.7). Regurgitation involving 1 of the semilunar (aortic or pulmonary) valves is usually also associated with some degree of stenosis; however, aortic regurgitation may be encountered in patients with a VSD directly under the aortic valve (supracristal VSD) and in patients with membranous subaortic stenosis.

In contrast to left-to-right shunts, in which intrinsic cardiac muscle function is generally either normal or increased, heart muscle function is decreased in the cardiomyopathies. Cardiomyopathies may affect systolic contractility or diastolic relaxation, or both. Decreased cardiac function results in increased atrial and ventricular filling pressure, and pulmonary edema occurs secondary to increased capillary pressure. Poor cardiac output leads to decreased organ blood flow, sympathetic activation, and the symptoms of poor perfusion and decreased urine output. The major causes of cardiomyopathy in infants and children include viral myocarditis, metabolic disorders, and genetic defects (see Chapter 439).

Lesions Resulting in Increased Pressure Load

The pathophysiologic common denominator of these lesions is an obstruction to normal blood flow. The most frequent are obstructions to ventricular outflow: valvular pulmonic stenosis, valvular aortic stenosis, and coarctation of the aorta (see Chapter 427). Less common are obstructions to ventricular inflow: tricuspid or mitral stenosis, cor triatriatum and obstruction of the pulmonary veins. Ventricular outflow obstruction can occur at the valve, below the valve (double-chambered right ventricle, subaortic membrane), or above it (branch pulmonary stenosis or supravalvular aortic stenosis). Unless the obstruction is severe, cardiac output will be maintained and the clinical symptoms of heart failure will be either subtle or absent. This compensation predominantly involves an increase in cardiac wall thickness (hypertrophy), but in later stages the affected chamber will begin to dilate and can progress to ventricular failure.

The clinical picture is different when obstruction to outflow is severe, which is usually encountered in the immediate newborn period. The infant may become critically ill within several hours of birth. Severe pulmonic stenosis in the newborn period (critical pulmonic stenosis) results in signs of right-sided heart failure (hepatomegaly, peripheral edema) as well as cyanosis from right-to-left shunting across the foramen ovale. Severe aortic stenosis in the newborn period (critical aortic stenosis) is characterized by signs of left-sided heart failure (pulmonary edema, poor perfusion) and right-sided failure (hepatomegaly, peripheral edema), and it may progress rapidly to total circulatory collapse. In older children, severe pulmonic stenosis leads to symptoms of right-sided heart failure, but usually not to cyanosis unless a pathway persists for right-to-left shunting (e.g., patency of the foramen ovale). Coarctation of the aorta in older children and adolescents is usually manifested as upper body hypertension and diminished pulses in the lower extremities. In the immediate newborn period, the presentation of coarctation can range from decreased pulses in the lower extremities to total circulatory collapse, depending on the severity of the narrowing. However, the clinical presentation of coarctation may be delayed because of the presence of a patent ductus arteriosus. In these patients, the open aortic end of the ductus may serve as a conduit for blood flow to partially bypass the obstruction or for blood leaving the right ventricle to directly supply the descending aorta (as it did in the fetus). These infants then become symptomatic, often dramatically, when the ductus finally closes, usually within the first few weeks of life.

Cyanotic Congenital Heart Lesions

This group of congenital heart lesions can also be further divided according to pathophysiology: whether pulmonary blood flow is decreased (tetralogy of Fallot, pulmonary atresia with an intact septum, tricuspid atresia, total anomalous pulmonary venous return with obstruction) or increased (transposition of the great vessels, single ventricle, truncus arteriosus, total anomalous pulmonary venous return without obstruction). The chest radiograph is a valuable tool for initial differentiation between these 2 categories.

Cyanotic Lesions with Decreased Pulmonary Blood Flow

These lesions must include both an obstruction to pulmonary blood flow (at the tricuspid valve or right ventricular or pulmonary valve level) and a pathway by which systemic venous blood can shunt from right to left and enter the systemic circulation (via a patent foramen ovale, atrial septal defect, or VSD). Common lesions in this group include tricuspid atresia, tetralogy of Fallot, and various forms of single ventricle with pulmonary stenosis (see Chapter 430). In these lesions, the degree of cyanosis depends on the degree of obstruction to pulmonary blood flow. If the obstruction is mild, cyanosis may be absent at rest. These patients may have hypcyanotic (“tel”) spells during conditions of stress. In contrast, if the obstruction is severe, pulmonary blood flow may be totally dependent on patency of the ductus arteriosus. When the ductus closes in the first few days of life, the neonate experiences profound hypoxemia and shock.

Cyanotic Lesions with Increased Pulmonary Blood Flow

This group of lesions is not associated with obstruction to pulmonary blood flow. Cyanosis is caused by either abnormal ventricular–arterial connections or total mixing of systemic venous and pulmonary venous blood within the heart (see Chapter 431). Transposition of the great vessels is the most common of the former group of lesions. In this condition, the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. Systemic venous blood returning to the right atrium is pumped directly back to the body and oxygenated blood returning from the lungs to the left atrium is pumped back into the lungs. The persistence of fetal pathways (foramen ovale and ductus arteriosus) allows for a small degree of mixing in the immediate newborn period; when the ductus begins to close, these infants can become extremely cyanotic.

Total mixing lesions include cardiac defects with a common atrium or ventricle, total anomalous pulmonary venous return, and truncus arteriosus (see Chapter 431). In this group, deoxygenated systemic venous blood and oxygenated pulmonary venous blood mix completely in the heart, and, as a result, oxygen saturation is equal in the pulmonary artery and aorta. If pulmonary blood flow is not obstructed, these infants have a combination of cyanosis and pulmonary overcirculation leading to heart failure. In contrast, if pulmonary stenosis is present, these infants may have cyanosis alone, similar to patients with tetralogy of Fallot.

Bibliography is available at Expert Consult.
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Atrial septal defects (ASDs) can occur in any portion of the atrial septum (secundum, primum, or sinus venosus), depending on which embryonic septal structure has failed to develop normally (see Chapter 420). Less commonly, the atrial septum may be nearly absent, with the creation of a functional single atrium. Isolated secundum ASDs account for ≈7% of congenital heart defects. The majority of cases of ASD are sporadic; autosomal dominant inheritance does occur as part of the Holt-Oram syndrome (hypoplastic or absent thumbs, radii, triphalangism, phocomelia, 1st-degree heart block, ASD) or in families with secundum ASD and heart block (see Table 424-2 in Chapter 424).

An isolated valve-incompetent patent foramen ovale (PFO) is a common echocardiographic finding during infancy. It is usually of no hemodynamic significance and is not considered an ASD; a PFO may play an important role if other structural heart defects are present. If another cardiac anomaly is causing increased right atrial pressure (pulmonary stenosis or atresia, tricuspid valve abnormalities, right ventricular dysfunction), venous blood may shunt across the PFO into the left atrium with resultant cyanosis. Because of the anatomic structure of the PFO, left-to-right shunting is unusual outside the immediate newborn period. In the presence of a large volume load or a hypertensive left atrium (secondary to mitral stenosis), the foramen ovale may be sufficiently dilated to result in a significant atrial left-to-right shunt. A valve-competent but probe-PFO may be present in 15-30% of adults. An isolated PFO does not require surgical treatment, although it may be a risk for paradoxical (right to left) systemic embolization. Device closure of these defects has been considered in young adults with a history of thromboembolic stroke.

Bibliography is available at Expert Consult.

Ostium Secundum Defect

An ostium secundum defect in the region of the fossa ovalis is the most common form of ASD and is associated with structurally normal atrioventricular (AV) valves. Mitral valve prolapse has been described in association with this defect but is rarely an important clinical consideration. Secundum ASDs may be single or multiple (fenestrated atrial septum), and openings ≥2 cm in diameter are common in symptomatic older children. Large defects may extend inferiorly toward the inferior vena cava and ostium of the coronary sinus, superiorly toward the superior vena cava, or posteriorly. Females outnumber males 3:1 in incidence. Partial anomalous pulmonary venous return, most commonly of the right upper pulmonary vein, may be an associated lesion.

PATHOPHYSIOLOGY

The degree of left-to-right shunting is dependent on the size of the defect, the relative compliance of the right and left ventricles, and the relative vascular resistance in the pulmonary and systemic circulations. In large defects, a considerable shunt of oxygenated blood flows from the left to the right atrium (Fig. 426-1). This blood is added to the usual venous return to the right atrium and is pumped by the right ventricle to the lungs. With large defects, the ratio of pulmonary to systemic blood flow (Qp:Qs) is usually between 2:1 and 4:1. The paucity of symptoms in infants with ASDs is related to the structure of the right ventricle in early life when its muscular wall is thick and less compliant, thus limiting the left-to-right shunt. As the infant becomes older and pulmonary vascular resistance drops, the right ventricular wall becomes thinner and the left-to-right shunt across the ASD increases. The increased blood flow through the right side of the heart results in enlargement of the right atrium and ventricle and dilation of the pulmonary artery. The left atrium may also be enlarged, but the left ventricle and aorta are normal in size. Despite the large pulmonary blood flow, pulmonary arterial pressure is usually normal because of the absence of a high-pressure communication between the pulmonary and systemic circulations. Pulmonary vascular resistance remains low throughout childhood, although it may begin to increase in adulthood and may eventually result in reversal of the shunt and clinical cyanosis.

CLINICAL MANIFESTATIONS

A child with an ostium secundum ASD is most often asymptomatic; the lesion is often discovered inadvertently during physical examination. Even an extremely large secundum ASD rarely produces clinically evident heart failure in childhood. However, on closer evaluation, in younger children, subtle failure to thrive may be present; in older children varying degrees of exercise intolerance may be noted. Often, the degree of limitation may go unnoticed by the family until after surgical repair, when the child’s growth or activity level increases.
Bibliography


markedly. Platypnea (dyspnea on standing, relieved when supine) and orthodeoxia (desaturation on standing, relieved when supine) may occur when right to left shunting occurs through an ASD.

The physical findings of an ASD are usually characteristic but fairly subtle and require careful examination of the heart, with special attention to the heart sounds. Examination of the chest may reveal a mild left precordial bulge. A right ventricular systolic lift may be palpable at the left sternal border. Sometimes a pulmonic ejection click can be heard. In most patients with an ASD, the characteristic finding is that the 2nd heart sound is widely split and fixed in its splitting during all phases of respiration. Normally, the duration of right ventricular ejection varies with respiration, with inspiration increasing right ventricular volume and delaying closure of the pulmonary valve. With an ASD, right ventricular diastolic volume is constantly increased and the ejection time is prolonged throughout all phases of respiration. A systolic ejection murmur is heard; it is medium pitched, without harsh qualities, seldom accompanied by a thrill, and best heard at the left middle and upper sternal border. It is produced by the increased flow across the right ventricular outflow tract into the pulmonary artery, not by low-pressure flow across the ASD. A short, rumbling mid-diastolic murmur produced by the increased volume of blood flow across the tricuspid valve is often audible at the lower left sternal border. This finding, which may be subtle and is heard best with the bell of the stethoscope, usually indicates a Qp:Qs ratio of at least 2:1.

**DIAGNOSIS**

The chest roentgenogram shows varying degrees of enlargement of the right ventricle and atrium, depending on the size of the shunt. The pulmonary artery is enlarged, and pulmonary vascularity is increased. These signs vary and may not be conspicuous in mild cases. Cardiac enlargement is often best appreciated on the lateral view because the right ventricle protrudes anteriorly as its volume increases. The electrocardiogram shows volume overload of the right ventricle; the QRS axis may be normal or exhibit right axis deviation, and a minor right ventricular conduction delay (rsR' pattern in the right precordial leads) may be present.

The echocardiogram shows findings characteristic of right ventricular volume overload, including an increased right ventricular end-diastolic dimension and flattening and abnormal motion of the ventricular septum (Fig. 426-2). A normal septum moves posteriorly during systole and anteriorly during diastole. With right ventricular overload and normal pulmonary vascular resistance, septal motion is either flattened or reversed—that is, anterior movement in systole. The location and size of the atrial defect are readily appreciated by 2-dimensional scanning, with a characteristic brightening of the echo image seen at the edge of the defect (T-artifact). The shunt is confirmed by pulsed and color flow Doppler. The normal entry of all pulmonary veins into the left atrium should be confirmed.

Patients with the classic features of a hemodynamically significant ASD on physical examination and chest radiography, in whom echocardiographic identification of an isolated secundum ASD is made, need not undergo diagnostic catheterization before repair, with the exception of an older patient, in whom pulmonary vascular resistance may be a concern. If pulmonary vascular disease is suspected, cardiac catheterization confirms the presence of the defect and allows measurement of the shunt ratio and pulmonary pressure and resistance. If catheterization is performed, usually at the time of device closure (see below), the oxygen content of blood from the right atrium will be much higher than that from the superior vena cava. This feature is not specifically diagnostic because it may occur with partial anomalous pulmonary venous return to the right atrium, with a ventricular septal defect (VSD) in the presence of tricuspid insufficiency, with AV septal defects associated with left ventricular to right atrial shunts, and with aorta to right atrial communications (ruptured sinus of Valsalva aneurysm). Pressure in the right side of the heart is usually normal, but small to moderate pressure gradients (<25 mm Hg) may be measured across the right ventricular outflow tract because of functional stenosis related to excessive blood flow. In children and adolescents, the pulmonary vascular resistance is almost always normal. The shunt is variable and depends on the size of the defect, but it may be of considerable volume (as high as 20 L/min/m²). Cineangiography, performed with the catheter through the defect and in the right upper pulmonary vein, demonstrates the defect and the location of the right upper pulmonary venous drainage. Alternatively, pulmonary angiography demonstrates the defect on the levophase (return of contrast to the left side of the heart after passing through the lungs).

**COMPLICATIONS**

Secundum ASDs are usually isolated, although they may be associated with partial anomalous pulmonary venous return, pulmonary valvular stenosis, VSD, pulmonary artery branch stenosis, and persistent left superior vena cava, as well as mitral valve prolapse and insufficiency. Secundum ASDs are associated with the autosomal dominant Holt-Oram syndrome. The gene responsible for this syndrome, situated in the region 12q21-q22 of chromosome 12, is TBX5, a member of the T-box transcriptional family. A familial form of secundum ASD associated with AV conduction delay has been linked to mutations in another transcription factor, Nkx2.5. Patients with familial ASD without heart block may carry a mutation in the transcription factor GATA4, located on chromosome 8p22-23 (see Table 424-2 in Chapter 424).

**TREATMENT**

Transcatheter or surgical device closure is advised for all symptomatic patients and also for asymptomatic patients with a Qp:Qs ratio of at least 2:1 or those with right ventricular enlargement. The timing for elective closure is usually after the 1st yr and before entry into school. Closure carried out at open heart surgery is associated with a mortality rate of <1%. Repair is preferred during early childhood because
surgical mortality and morbidity are significantly greater in adulthood; the long-term risk of arrhythmia is also greater after ASD repair in adults. For most patients, the procedure of choice is percutaneous catheter device closure using an atrial septal occlusion device, implanted transvenously in the cardiac catheterization laboratory (Fig. 426-3). The results are excellent and patients are discharged the following day. With the latest generation of devices, the incidence of serious complications such as device erosion is 0.1% and can be decreased by identifying high-risk patients such as those with a deficient rim of septum around the device. Echocardiography can usually determine whether a patient is a good candidate for device closure. In patients with small secundum ASDs and minimal left-to-right shunts without right ventricular enlargement, the consensus is that closure is not required. It is unclear at present whether the persistence of a small ASD into adulthood increases the risk for stroke enough to warrant prophylactic closure of all these defects.

**PROGNOSIS**

Small- to moderate-sized ASDs detected in term infants may close spontaneously. Secundum ASDs are well tolerated during childhood, and symptoms do not usually appear until the 3rd decade or later. Pulmonary hypertension, atrial dysrhythmias, tricuspid or mitral insufficiency, and heart failure are late manifestations; these symptoms may initially appear during the increased volume load of pregnancy. Infective endocarditis is extremely rare, and antibiotic prophylaxis for isolated secundum ASDs is not recommended.

The results after surgical or device closure in children with moderate to large shunts are excellent. Symptoms disappear rapidly, and growth is frequently enhanced. Heart size decreases to normal, and the electrocardiogram shows decreased right ventricular forces. Late right-heart failure and arrhythmias are less frequent in patients who have had early repair, becoming more common in patients who undergo surgery after 20 yr of age. Although early and midterm results with device closure are excellent, the long-term effects are not yet known. Reports of resolution of migraine headaches in patients after device closure of ASD or PFO are intriguing, suggesting a possible thromboembolic etiology; there are also paradoxical reports of patients whose migraines began or worsened after placement of one of these devices.

### 426.3 Sinus Venosus Atrial Septal Defect

**Daniel Bernstein**

A sinus venosus ASD is situated in the upper part of the atrial septum in close relation to the entry of the superior vena cava. Often, 1 or more pulmonary veins (usually from the right lung) drain anomalously into the superior vena cava. The superior vena cava sometimes straddles the defect; in this case, some systemic venous blood enters the left atrium, but only rarely does it cause clinically evident cyanosis. The hemodynamic disturbance, clinical picture, electrocardiogram, and roentgenogram are similar to those seen in secundum ASD. The diagnosis can usually be made by 2-dimensional echocardiography. If there are questions regarding pulmonary venous drainage, cardiac CT or MRI is usually diagnostic. Cardiac catheterization is rarely required, with the exception being in adult patients where assessment of pulmonary vascular resistance may be important. Anatomic correction generally requires the insertion of a patch to close the defect while incorporating the entry of anomalous veins into the left atrium. If the anomalous vein drains high in the superior vena cava, the vein can be left intact and the ASD closed to incorporate the mouth of the superior vena cava into the left atrium. The superior vena cava proximal to the venous entrance is then detached and anastomosed directly to the right atrium. This procedure avoids direct suturing of the pulmonary vein with less chance of future stenosis. Surgical results are generally excellent. Rarely, sinus venosus defects involve the inferior vena cava.

### 426.4 Partial Anomalous Pulmonary Venous Return

**Daniel Bernstein**

One or several pulmonary veins may return anomalously to the superior or inferior vena cava, the right atrium, or the coronary sinus and produce a left-to-right shunt of oxygenated blood. Partial anomalous pulmonary venous return usually involves some or all of the veins from only 1 lung, more often the right one. When an associated ASD is present, it is generally of the sinus venosus type, although can be of the secundum type (see Chapters 426.2 and 426.3). When an ASD is detected by echocardiography, one must always search for associated partial anomalous pulmonary venous return. The history, physical signs, and electrocardiographic and radiologic findings are indistinguishable from those of an isolated ostium secundum ASD. Occasionally, an anomalous vein draining into the inferior vena cava is visible on chest radiography as a crescentic shadow of vascular density along the right border of the cardiac silhouette (scimitar syndrome); in these cases, an ASD is not usually present, but pulmonary sequestration or ipsilateral lung hypoplasia and anomalous arterial supply to that lobe are common findings. Total anomalous pulmonary venous return is a cyanotic lesion and is discussed in Chapter 431.7. Echocardiography generally confirms the diagnosis. MRI and CT are also useful if there

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Figure 426-3 Intravascular ultrasound imaging of transcatheter occlusion of an atrial septal defect. A, A catheter (small arrow) has been advanced across the atrial defect, and the left-sided disk of the device (large arrow) has been extruded from the sheath into the left atrium (LA). B, The right atrial disk (arrow) has now been extruded into the right atrium (RA). The 2 halves of the device are then locked together and the catheter detached from the occluder device and removed.
is a question regarding pulmonary venous drainage or in cases of scimitar syndrome. If cardiac catheterization is performed, the presence of anomalous pulmonary veins is demonstrated by selective pulmonary arteriography and anomalous pulmonary arterial supply to the right lung is demonstrated by descending aortography.

The prognosis is excellent, similar to that for ostium secundum ASDs. When a large left-to-right shunt is present, surgical repair is performed. The associated ASD should be closed in such a way that pulmonary venous return is directed to the left atrium. A single anomalous pulmonary vein without an atrial communication may be difficult to redirect to the left atrium; if the shunt is small, it may be left unoperated.

### 426.5 Atrioventricular Septal Defects (Ostium Primum and Atrioventricular Canal or Endocardial Cushion Defects)

Daniel Bernstein

The abnormalities encompassed by AV septal defects are grouped together because they represent a spectrum of a basic embryologic abnormality, a deficiency of the AV septum. An ostium primum defect is situated in the lower portion of the atrial septum and overlies the mitral and tricuspid valves. In most instances, a cleft in the anterior leaflet of the mitral valve is also noted. The tricuspid valve is usually functionally normal, although some anatomic abnormality of the septal leaflet is present. The ventricular septum is intact.

An AV septal defect, also known as an AV canal defect or an endocardial cushion defect, consists of contiguous atrial and VSDs with markedly abnormal AV valves. The severity of the valve abnormalities varies considerably; in the complete form of AV septal defect, a single AV valve is common to both ventricles and consists of an anterior and a posterior bridging leaflet related to the ventricular septum, with a lateral leaflet in each ventricle. The lesion is common in children with Down syndrome.

Transitional varieties of these defects also occur and include ostium primum defects with clefts in the anterior mitral and septal tricuspid valve leaflets and small VSDs, and, less commonly, ostium primum defects with normal AV valves. In some patients, the atrial septum is intact, but an inlet VSD is similar to that found in the full AV septal defect. Sometimes AV septal defects are associated with varying degrees of hypoplasia of one of the ventricles, known as either left- or right-dominant atrioventricular septal defect. If the affected ventricular chamber is too small to establish a 2-ventricle circulation, then surgical palliation, aiming for an eventual Fontan procedure, is performed (see Chapters 430.4 and 431.10).

### PATHOPHYSIOLOGY

The basic abnormality in patients with ostium primum defects is the combination of a left-to-right shunt across the atrial defect and mitral (or occasionally tricuspid) insufficiency. The shunt is usually moderate to large, the degree of mitral insufficiency is generally mild to moderate, and pulmonary arterial pressure is typically normal or only mildly increased. The physiology of this lesion is, therefore, similar to that of an ostium secundum ASD.

In complete AV septal defects, the left-to-right shunt occurs at both the atrial and ventricular levels (Fig. 426-4). Additional shunting may occur directly from the left ventricle to the right atrium because of absence of the AV septum. Pulmonary hypertension and an early tendency to increase pulmonary vascular resistance are common. AV valvular insufficiency increases the volume load on one or both ventricles. If the defect is large enough, some right-to-left shunting may also occur at both the atrial and ventricular levels and lead to mild arterial desaturation. With time, progressive pulmonary vascular disease increases the right-to-left shunt so that clinical cyanosis develops (Eisenmenger physiology; see Chapter 433.2).

### CLINICAL MANIFESTATIONS

Many children with ostium primum defects are asymptomatic, and the anomaly is discovered during a general physical examination. In patients with moderate shunts and mild mitral insufficiency, the physical signs are similar to those of the secundum ASD, but with an additional apical holosystolic murmur caused by mitral insufficiency.

A history of exercise intolerance, easy fatigability, and recurrent pneumonia may be obtained, especially in infants with large left-to-right shunts and severe mitral insufficiency. In these patients, cardiac enlargement is moderate or marked, and the precordium is hyperdynamic. Auscultatory signs produced by the left-to-right shunt include a normal or accentuated 1st heart sound; wide, fixed splitting of the 2nd sound; a pulmonary systolic ejection murmur sometimes preceded by a click; and a low-pitched, mid-diastolic rumbling murmur at the lower left sternal edge or apex, or both, as a result of increased flow through the AV valves. Mitral insufficiency may be manifested by a harsh (occasionally very high pitched) apical holosystolic murmur that radiates to the left axilla.

With complete AV septal defects, heart failure and intercurrent pulmonary infection usually appear in infancy. The liver is enlarged and the infant shows signs of failure to thrive. Cardiac enlargement is moderate to marked, and a systolic thrill is frequently palpable at the lower left sternal border. A precordial bulge and lift may be present as well. The 1st heart sound is normal or accentuated. The 2nd heart sound is widely split if the pulmonary flow is massive. A low-pitched, mid-diastolic rumbling murmur is audible at the lower left sternal border, and a pulmonary systolic ejection murmur is produced by the large pulmonary flow. The harsh apical holosystolic murmur of mitral insufficiency may also be present.
DIAGNOSIS

Chest radiographs of children with complete AV septal defects often show moderate to severe cardiac enlargement caused by the prominence of both ventricles and atria. The pulmonary artery is large, and pulmonary vascularity is increased.

The electrocardiogram in patients with a complete AV septal defect is distinctive. The principal abnormalities are (1) superior orientation of the mean frontal QRS axis with left axis deviation to the left upper or right upper quadrant, (2) counterclockwise inscription of the superiorly oriented QRS vector loop (often manifest by a Q wave in leads I and aVL), (3) signs of biventricular hypertrophy or isolated right ventricular hypertrophy, (4) right ventricular conduction delay (rSR’ pattern in leads V1, V6, and V3), (5) normal or tall P waves, and (6) occasional prolongation of the P-R interval (Fig. 426-5).

The echocardiogram (Fig. 426-6) is diagnostic and shows signs of right ventricular enlargement with encroachment of the mitral valve echo on the left ventricular outflow tract; the abnormally low position of the AV valves results in a "goose neck" deformity of the left ventricular outflow tract. In normal hearts, the tricuspid valve inserts slightly more toward the apex than the mitral valve does. In AV septal defects, both valves insert at the same level because of absence of the AV septum. In complete AV septal defects, the ventricular septum is also deficient and the common AV valve is readily appreciated. Pulsed and color flow Doppler echocardiography will demonstrate left-to-right shunting at the atrial, ventricular, or left ventricular to right atrial levels and can be used to semiquantitate the degree of AV valve insufficiency. Echocardiography is useful for determining the insertion points of the chordae of the common AV valve and for evaluating the presence of associated lesions such as patent ductus arteriosus (PDA) or coarctation of the aorta.

Cardiac catheterization and angiography is rarely required to confirm the diagnosis unless pulmonary vascular disease is suspected, such as in a patient in whom diagnosis has been delayed beyond early infancy, especially in those with Down syndrome in whom the development of pulmonary vascular disease may be more rapid. Catheterization demonstrates the magnitude of the left-to-right shunt, the degree of elevation of pulmonary vascular resistance, and the severity of insufficiency of the common AV valve. By oximetry, the shunt is usually demonstrable at both the atrial and ventricular levels. Arterial oxygen saturation is normal or only mildly reduced unless severe pulmonary vascular disease is present. Children with ostium primum defects generally have normal or only moderately elevated pulmonary arterial pressure. Conversely, complete AV septal defects are associated with right ventricular and pulmonary hypertension and, in older patients, with increased pulmonary vascular resistance (see Chapter 433.2).

Selective left ventriculography will demonstrate deformity of the mitral or common AV valve and the distortion of the left ventricular outflow tract caused by this valve (goose neck deformity). The abnormal anterior leaflet of the mitral valve is serrated, and mitral insufficiency is noted, usually with regurgitation of blood into both the left and right atria. Direct shunting of blood from the left ventricle to the right atrium may also be demonstrated.

TREATMENT

Ostium primum defects are approached surgically from an incision in the right atrium. The cleft in the mitral valve is located through the atrial defect and is repaired by direct suture. The defect in the atrial septum is usually closed by insertion of a patch prosthesis. The surgical mortality rate for ostium primum defects is very low.

Surgical treatment of complete AV septal defects is more difficult, although still highly successful. The postoperative course may be prolonged in infants with severe cardiac failure and in those with pulmonary hypertension. Because of the risk of pulmonary vascular disease developing as early as 6-12 mo of age, surgical intervention must be performed during infancy. Full correction of these defects can be readily accomplished in infancy; palliation with pulmonary arterial banding, once more common, is reserved for the small subset of patients who have other associated lesions that make early corrective surgery too risky. The atrial and ventricular defects are patched and the AV valves reconstructed. Complications include surgically induced heart block requiring placement of a permanent pacemaker, excessive narrowing of the left ventricular outflow tract requiring surgical revision, and residual tricuspid or mitral regurgitation, which long-term can require replacement with a prosthetic valve.

Figure 426-5 Electrocardiogram from a child with an atrioventricular septal defect. Note the QRS axis of −60 degrees and the right ventricular conduction delay with an RSR’ pattern in V1 and V6 (V1 and V6 paper speed = 50 mm/sec).

Figure 426-6 Echocardiogram of an atrioventricular septal defect. A, Subcostal 4-chamber view demonstrating the common atrioventricular valve (arrows) spanning the atrial and ventricular septal defects. B, Doppler imaging shows 2 jets of regurgitation through the left side of the common atrioventricular valve (arrows). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
PROGNOSIS
The prognosis for unrepaired complete AV septal defects depends on the magnitude of the left-to-right shunt, the degree of elevation of pulmonary vascular resistance, and the severity of AV valve insufficiency. Death from cardiac failure during infancy used to be frequent before the advent of early corrective surgery. In patients who survived without surgery, pulmonary vascular obstructive disease usually developed. Most patients with ostium primum defects and minimal AV valve involvement are asymptomatic or have only minor, nonprogressive symptoms until they reach the 3rd-4th decade of life, similar to the course of patients with secundum ASDs. Late postoperative complications include atrial arrhythmias and heart block, progressive narrowing of the left ventricular outflow tract requiring surgical revision, and eventual worsening of AV valve regurgitation (usually on the left side) requiring replacement with a prosthetic valve.

Bibliography is available at Expert Consult.

426.6 Ventricular Septal Defect
Daniel Bernstein

VSD is the most common cardiac malformation and accounts for 25% of congenital heart disease. Defects may occur in any portion of the ventricular septum, but most are of the membranous type. These defects are in a posteroinferior position, anterior to the septal leaflet of the tricuspid valve. VSDs between the crista supraventricularis and the papillary muscle of the conus may be associated with pulmonary stenosis and other manifestations of tetralogy of Fallot (see Chapter 430.1). VSDs superior to the crista supraventricularis (supracristal) are less common; they are found just beneath the pulmonary valve and may impinge on an aortic sinus and cause aortic insufficiency. VSDs in the midportion or apical region of the ventricular septum are muscular in type and may be single or multiple (Swiss cheese septum).

PATHOPHYSIOLOGY
The physical size of the VSD is a major, but not the only, determinant of the size of the left-to-right shunt. The level of pulmonary vascular resistance in relation to systemic vascular resistance also determines the shunt’s magnitude. When a small communication is present (usually <5 mm), the VSD is pressure restrictive, meaning that right ventricular pressure is normal. The higher pressure in the left ventricle drives the shunt left to right and the size of the defect limits the magnitude of the shunt. In large nonrestrictive VSDs (usually >10 mm), right and left ventricular pressures are equalized. In these defects, the direction of shunting and the shunt magnitude are determined by the ratio of pulmonary to systemic vascular resistance (Fig. 426-7).

After birth in patients with a large VSD, pulmonary vascular resistance may remain elevated, delaying the normal postnatal decrease, and thus the size of the left-to-right shunt may initially be limited. Because of normal involution of the media of small pulmonary arteries, pulmonary vascular resistance begins to fall in the 1st few wk after birth and the size of the left-to-right shunt increases. Eventually, a large left-to-right shunt develops, and clinical symptoms become apparent. In most cases during early infancy, pulmonary vascular resistance is only slightly elevated, and the major contribution to pulmonary hypertension is the large communication allowing exposure of the pulmonary circulation to systemic pressure and the large pulmonary blood flow. With continued exposure of the pulmonary vascular bed to high systolic pressure and high flow, pulmonary vascular obstructive disease eventually develops. When the ratio of pulmonary to systemic resistance approaches 1:1, the shunt becomes bidirectional, signs of heart failure abate, and the patient begins to show signs of cyanosis (Eisenmenger physiology; see Chapter 433.2). In rare infants with a large VSD, usually those with Down syndrome, pulmonary vascular resistance never decreases, and symptoms may remain minimal until Eisenmenger physiology becomes evident.

The magnitude of intracardiac shunts is usually described by the Qp:Qs ratio. If the left-to-right shunt is small (Qp:Qs < 1.5:1), the cardiac chambers are not appreciably enlarged and the pulmonary vascular bed is probably normal. If the shunt is large (Qp:Qs > 2:1), left atrial and ventricular volume overload occurs, as does right ventricular and pulmonary arterial hypertension. The main pulmonary artery, left atrium, and left ventricle are enlarged.

CLINICAL MANIFESTATIONS
The clinical findings of patients with a VSD vary according to the size of the defect and pulmonary blood flow and pressure. Small VSDs with trivial left-to-right shunts and normal pulmonary arterial pressure are the most common. These patients are asymptomatic, and the cardiac lesion is usually found during routine physical examination. Characteristically, a loud, harsh, or blowing holosystolic murmur is present and heard best over the lower left sternal border, and it is frequently accompanied by a thrill. In a few instances, the murmur ends before the 2nd sound, presumably because of closure of the defect during late systole. A short, harsh systolic murmur localized to the apex in a neonate is often a sign of a tiny VSD in the apical muscular septum. In premature infants, the murmur may be heard early because pulmonary vascular resistance decreases more rapidly.

Large VSDs with excessive pulmonary blood flow and pulmonary hypertension are responsible for dyspnea, feeding difficulties, poor growth, profuse perspiration, recurrent pulmonary infections, and cardiac failure in early infancy. Cyanosis is usually absent, but duskeness is sometimes noted during infections or crying. Prominence of the left precordium is common, as are a palpable parasternal lift, a laterally displaced apical impulse and apical thrust, and a systolic thrill. The holosystolic murmur of a large VSD is generally less harsh than that of a small VSD and more blowing in nature because of the absence of a significant pressure gradient across the defect. It is even less likely to be prominent in the newborn period. The pulmonic component of
Bibliography
the 2nd heart sound may be increased as a result of pulmonary hypertension. The presence of a mid-diastolic, low-pitched rumble at the apex is caused by increased blood flow across the mitral valve and usually indicates a Qp:Qs ratio of ≥2:1. This murmur is best appreciated with the bell of the stethoscope.

**DIAGNOSIS**

In patients with small VSDs, the chest x-ray is usually normal, although minimal cardiomegaly and a borderline increase in pulmonary vasculature may be observed. The electrocardiogram is generally normal but may suggest left ventricular hypertrophy. The presence of left ventricular hypertrophy is a warning that the defect is not small and that the patient has pulmonary hypertension or an associated lesion such as pulmonic stenosis. In large VSDs, the chest x-ray shows gross cardiomegaly with prominence of both ventricles, the left atrium, and the pulmonary artery (Fig. 426-8). Pulmonary vascular markings are increased, and frank pulmonary edema, including pleural effusions, may be present. The electrocardiogram shows biventricular hypertrophy; P waves may be notched or peaked.

The 2-dimensional echocardiogram (Fig. 426-9) shows the position and size of the VSD. In small defects, especially those of the muscular septum, the defect itself may be difficult to image and is visualized only by color Doppler examination. In defects of the membranous septum, a thin membrane (called a ventricular septal aneurysm but consisting of tricuspid valve tissue) can partially cover the defect and limit the volume of the left-to-right shunt. Echocardiography is also useful for estimating shunt size by examining the degree of volume overload of the left atrium and left ventricle; in the absence of associated lesions, the extent of their increased dimensions is a good reflection of the size of the left-to-right shunt. Pulsed Doppler examination shows whether the VSD is pressure restrictive by calculating the pressure gradient across the defect. Such calculation allows an estimation of right ventricular pressure and helps determine whether the patient is at risk for the development of early pulmonary vascular disease. The echocardiogram can also be useful to determine the presence of aortic valve insufficiency or aortic leaflet prolapse in the case of supracristal VSDs.

The hemodynamics of a VSD can also be demonstrated by cardiac catheterization, although catheterization is today performed only when laboratory data do not fit well with the clinical findings or when pulmonary vascular disease is suspected. Oximetry demonstrates increased oxygen content in the right ventricle; because some defects eject blood almost directly into the pulmonary artery (streaming), the full magnitude of the oxygen saturation increase is occasionally apparent only when pulmonary arterial blood is sampled. Small, restrictive VSDs are associated with normal right-heart pressures and pulmonary vascular resistance. Large, nonrestrictive VSDs are associated with equal or nearly equal pulmonary and systemic systolic pressure and variable elevations in pulmonary vascular resistance. Pulmonary blood flow may be 2–4 times systemic blood flow. In patients with such “hyperdynamic pulmonary hypertension,” pulmonary vascular resistance is only minimally elevated because resistance is equal to pressure divided by flow. However, if left untreated until Eisenmenger syndrome is present, pulmonary artery systolic and diastolic pressure will be elevated but the degree of left-to-right shunting minimal. In these cases, desaturation of blood in the left ventricle is usually encountered.

![Figure 426-8](image1)

*Figure 426-8* A, Preoperative radiograph in a patient with a ventricular septal defect with a large left-to-right shunt and pulmonary hypertension. Significant cardiomegaly, prominence of the pulmonary arterial trunk, and pulmonary overcirculation are evident. B, Three years after surgical closure of the defect, heart size is markedly decreased, and the pulmonary vasculature is normal.

![Figure 426-9](image2)

*Figure 426-9* Echocardiogram in a patient with a perimembranous ventricular septal defect. A, Apical 4-chamber view showing the location of the defect (outlined between 2 crosshatches) beneath the aortic valve. B, Color Doppler imaging shows the left-to-right shunt (arrow) through the defect (the red color represents blood moving toward the ultrasound transducer and does not indicate the level of oxygenation of the blood). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
The size, location, and number of ventricular defects can be demonstrated by left ventriculography. Contrast medium passes across the defect or defects to opacify the right ventricle and pulmonary artery. Administration of 100% oxygen with and without nitric oxide can be used to determine whether the pulmonary vascular resistance, if elevated, is still reactive and therefore more likely to drop after surgical repair.

**TREATMENT**

The natural course of a VSD depends to a large degree on the size of the defect. A significant number (30-50%) of small defects close spontaneously, most frequently during the 1st 2 yr of life. Small muscular VSDs are more likely to close (up to 80%) than membranous VSDs (up to 35%). The vast majority of defects that close do so before the age of 4 yr, although spontaneous closure has been reported in adults. VSDs that close often have ventricular septal aneurysm (accessory tricuspid valve) tissue that limits the magnitude of the shunt. Most children with small restrictive defects remain asymptomatic, without evidence of an increase in heart size, pulmonary arterial pressure, or resistance; a long-term risk is infective endocarditis. Some long-term studies of adults with unoperated small VSDs show an increased incidence of arrhythmia, subaortic stenosis, and exercise intolerance. Guidelines from the Council on Cardiovascular Disease in the Young of the American Heart Association state that an isolated, small, hemodynamically insignificant VSD is not an indication for surgery. However, the declining risk of open heart surgery has led some to suggest that all VSDs be closed electively by mid-childhood.

It is less common for moderate or large VSDs to close spontaneously, although even defects large enough to result in heart failure may become smaller and up to 8% may close completely. More commonly, infants with large defects have repeated episodes of respiratory infection and heart failure despite optimal medical management. Heart failure may be manifested in many of these infants primarily as failure to thrive. Pulmonary hypertension occurs as a result of high pulmonary blood flow. These patients are at risk for pulmonary vascular disease if the defect is not repaired during early infancy.

Patients with VSD are also at risk for the development of aortic valve regurgitation, the greatest risk occurring in patients with a supracristal VSD (see Chapter 426.7). A small number of patients with VSD develop acquired infundibular pulmonary stenosis, which then protects the pulmonary circulation from the short-term effects of pulmonary overcirculation and the long-term effects of pulmonary vascular disease. In these patients, the clinical picture changes from that of a VSD with a large left-to-right shunt to a VSD with pulmonary stenosis. The shunt may diminish in size, become balanced, or even become a net right-to-left shunt. These patients must be carefully distinguished from those in whom an Eisenmenger physiology develops (see Chapter 433.2).

In patients with small VSDs, parents should be reassured of the relatively benign nature of the lesion, and the child should be encouraged to live a normal life, with no restrictions on physical activity. Surgical repair is not recommended. As protection against infective endocarditis, the integrity of primary and permanent teeth should be carefully maintained; with the latest revision of the American Heart Association guidelines, antibiotic prophylaxis is no longer recommended for dental visits or surgical procedures (see Chapter 437). These patients can be monitored by a combination of clinical examination and noninvasive laboratory tests until the VSD has closed spontaneously. Echocardiography is used to estimate pulmonary artery pressure, screen for the development of left ventricular outflow tract pathology (subaortic membrane or aortic regurgitation), and to confirm spontaneous closure.

In infants with a large VSD, management has 2 aims: to get the symptoms of heart failure under control (see Chapter 442) and prevent the development of pulmonary vascular disease. If early treatment is successful, sometimes the shunt may diminish in size with spontaneous improvement, especially during the 1st yr of life. The clinician must be alert not to confuse clinical improvement caused by a decrease in defect size with clinical changes caused by the development of Eisenmenger physiology. Because catheter or surgical closure can be carried out at low risk in most infants, medical management should not be pursued in symptomatic infants after an initial unsuccessful trial. Because pulmonary vascular disease can usually be prevented when surgery is performed within the 1st yr of life, even infants with well-controlled heart failure should not have surgery delayed inordinately unless there is evidence that the defect is becoming pressure restrictive.

Indications for surgical closure of a VSD include patients at any age with large defects in whom clinical symptoms and failure to thrive cannot be controlled medically; infants between 6 and 12 mo of age with large defects associated with pulmonary hypertension, even if the symptoms are controlled by medication; and patients older than 24 mo with a Qp:Qs ratio greater than 2:1. Patients with a supracristal VSD of any size are usually referred for surgery because of the high risk for aortic valve regurgitation (see Chapter 426.7). Severe pulmonary vascular disease nonresponsive to pulmonary vasodilators is a contraindication to closure of a VSD.

Transcatheter occlusion closure is most successful in treating muscular VSDs, which may be difficult to access by surgery. Perimembranous VSD catheter closure has a high risk of postprocedure heart block and is not recommended. Hybrid methods employing a sternotomy with device placement through the anterior wall of the right ventricle under transesophageal echo and fluoroscopic visualization has been performed in difficult to approach muscular defects.

**PROGNOSIS**

The results of primary surgical repair are excellent, and complications leading to long-term problems (residual ventricular shunts requiring reoperation or heart block requiring a pacemaker) are rare. Pulmonary arterial palliative banding with repair in later childhood, once the standard of care, is now reserved for extremely complicated cases or very premature infants. Surgical risks are somewhat higher for defects in the muscular septum, particularly apical defects and multiple (Swiss cheese–type) VSDs. These patients may require pulmonary arterial banding if symptomatic, with subsequent debanding and repair of multiple VSDs at an older age.

After surgical obliteration of the left-to-right shunt, the hyperdynamic heart becomes quiet, cardiac size decreases toward normal (see Fig. 426-8), thrills and murmurs are abolished, and pulmonary artery hypertension regresses. The patient’s clinical status improves markedly. Most infants begin to thrive, and cardiac medications are no longer required. Catch-up growth occurs in most patients within the next 1-2 yr. In some instances after successful surgery, systolic ejection murmurs of low intensity persist for months. The long-term prognosis after surgery is excellent. Patients with a small VSD and those who have undergone surgical closure without residua are considered to be at standard risk for health and life insurance.

Bibliography is available at Expert Consult.

### 426.7 Supracristal Ventricular Septal Defect with Aortic Insufficiency

**Daniel Bernstein**

A supracristal VSD is complicated by prolapse of the aortic valve into the defect and aortic insufficiency, which may eventually develop in 50-90% of these patients. Although supracristal VSD accounts for ≈5% of all patients with VSD, the incidence is higher in Asian children and in males. The VSD, which may be small or moderate in size, is located anterior to and directly below the pulmonary valve in the outlet septum, superior to the muscular ridge known as the crista supraventricularis, which separates the trabecular body of the right ventricle from the smooth outflow portion. The right or, less often, the noncoronary aortic cusp prolapses into the defect and may partially or even completely occlude it. Such occlusion may limit the amount of left-to-right shunting and give the false impression that the defect is not large.
Bibliography
Aortic insufficiency is most often not recognized until 5-9 yr life or beyond. Of note, aortic insufficiency is occasionally associated with VSDs located in the membranous septum.

Early heart failure secondary to a large left-to-right shunt rarely occurs, but without surgery, severe aortic insufficiency and left ventricular failure may ensue. The murmur of a supravalvular VSD is usually heard at the mid to upper left sternal border, as opposed to the lower left sternal border, and it is sometimes confused with that of pulmonary stenosis. A decrescendo diastolic murmur will be appreciated at the upper right or mid left sternal borders if there is aortic insufficiency. More advanced degrees of aortic insufficiency will be associated with a wide pulse pressure and a hyperdynamic precordium. These clinical findings must be distinguished from PDA or other defects associated with aortic runoff.

The clinical manifestations vary widely from trivial aortic regurgitation and small left-to-right shunts in asymptomatic children to florid aortic insufficiency and massive cardiomegaly in symptomatic adolescents. Closure of all supravalvular ventricular VSDs at the time of diagnosis is commonly recommended to prevent the development of aortic regurgitation, even in an asymptomatic child. Patients who already have significant aortic insufficiency require surgical intervention to prevent irreversible left ventricular dysfunction. Surgical options depend on the degree of damage to the valve. If the insufficiency is mild, they may include simple closure of the defect to bolster the valve apparatus without touching the valve itself, valvuoplasty for more significant degrees of involvement, and replacement with a prosthesis or homograft or aortopulmonary translocation for severe involvement.

### 426.8 Patent Ductus Arteriosus

Daniel Bernstein

During fetal life, most of the pulmonary arterial blood is shunted right-to-left through the ductus arteriosus into the aorta (see Chapter 421). Functional closure of the ductus normally occurs soon after birth, but if the ductus remains patent when pulmonary vascular resistance falls, aortic blood then is shunted left-to-right into the pulmonary artery. The aortic end of the ductus is just distal to the origin of the left subclavian artery, and the ductus enters the pulmonary artery at its bifurcation. Female patients with PDA outnumber males 2:1. PDA is also associated with maternal rubella infection during early pregnancy, an uncommon occurrence. PDA is a common problem in premature infants, as the smooth muscle in the wall of the preterm ductus is less responsive to high PO₂ and therefore less likely to constrict after birth. In these infants, it can cause severe hemodynamic derangements and several major sequelae (see Chapter 101.3). When a term infant is found to have a PDA, the wall of the ductus is deficient in both the mucoid endothelial layer and the muscular media, whereas in the premature infant, the PDA usually has a normal structure. Thus, a PDA persisting beyond the 1st few wk of life in a term infant rarely closes spontaneously or with pharmacologic intervention, whereas if early pharmacologic or surgical intervention is not required in a premature infant, spontaneous closure occurs in most instances. A PDA is seen in 10% of patients with other congenital heart lesions and often plays a critical role in providing a source of pulmonary blood flow when the right ventricular outflow tract is stenotic or atretic (see Chapter 430) or in providing systemic blood flow in the presence of aortic coarctation or interruption (see Chapters 426.6 to 427.8).

### PATHOPHYSIOLOGY

As a result of the higher aortic pressure postnatally, blood shunts left to right through the ductus, from the aorta to the pulmonary artery. The extent of the shunt depends on the size of the ductus and on the ratio of pulmonary to systemic vascular resistance. If the PDA is small, pressures within the pulmonary artery, the right ventricle, and the right atrium are normal. If the PDA is large, pulmonary artery pressure may be elevated to systemic levels during both systole and diastole. Thus, patients with a large PDA are at high risk for the development of pulmonary vascular disease if left unoperated.

### CLINICAL MANIFESTATIONS

A small PDA is usually asymptomatic. A large PDA will result in heart failure similar to that encountered in infants with a large VSD. Retardation of physical growth may be a major manifestation in infants with large shunts. A small PDA is associated with normal peripheral pulses, and a large PDA results in bounding peripheral arterial pulses and a wide pulse pressure, due to runoff of blood into the pulmonary artery during diastole. The heart is normal in size when the ductus is small, but moderately or grossly enlarged in cases with a large communication. In these cases, the apical impulse is prominent and, with cardiac enlargement, is heaving. A thrill, maximal in the 2nd left interspace, is often present and may radiate toward the left clavicle, down the left sternal border, or toward the apex. It is usually systolic but may also be palpated throughout the cardiac cycle. The classic continuous murmur is described as being like machinery in quality. It begins soon after onset of the 1st sound, reaches maximal intensity at the end of systole, and wanes in late diastole. It may be localized to the 2nd left intercostal space or radiate down the left sternal border or to the left clavicle. When pulmonary vascular resistance is increased, the diastolic component of the murmur may be less prominent or absent. In patients with a large left-to-right shunt, a low-pitched mitral mid-diastolic murmur may be audible at the apex as a result of the increased volume of blood flow across the mitral valve.

### DIAGNOSIS

If the left-to-right shunt is small, the electrocardiogram is normal; if the ductus is large, left ventricular or biventricular hypertrophy is present. The diagnosis of an isolated, uncomplicated PDA is untenable when right ventricular hypertrophy is present.

Radiographic studies in patients with a large PDA show a prominent pulmonary artery with increased pulmonary vascular markings. Cardiac size depends on the degree of left-to-right shunting; it may be normal or moderately to markedly enlarged. The chambers involved are the left atrium and left ventricle. The aortic knob may be normal or prominent.

On echocardiogram, the cardiac chambers will be normal in size if the ductus is small. With large shunts, left atrial and left ventricular dimensions are increased. The ductus can easily be visualized directly and its size estimated. Color and pulsed Doppler examinations demonstrate systolic or diastolic (or both) retrograde turbulent flow in the pulmonary artery, and aortic retrograde flow in diastole (Fig. 426-10) in the presence of a large shunt.

The clinical signs and echocardiographic findings are sufficiently distinctive to allow an accurate diagnosis by noninvasive methods in most patients. In rare patients with atypical findings, cardiac catheterization may be indicated for confirmation of diagnosis. Cardiac catheterization will demonstrate either normal or increased pressure in the right ventricle and pulmonary artery, depending on the size of the ductus. The presence of oxygenated blood shunting into the pulmonary artery confirms the left-to-right shunt. The catheter may pass from the pulmonary artery through the ductus into the descending aorta. Injection of contrast medium into the ascending aorta shows opacification of the pulmonary artery from the aorta and identifies the ductus.

Other conditions can produce systolic and diastolic murmurs in the pulmonic area in an acyanotic patient and are described in Chapter 422. An aortopulmonary window defect may rarely be clinically indistinguishable from a patent ductus, although, in most cases, the murmur is only systolic and is loudest at the right rather than the left upper sternal border. A sinus of Valsalva aneurysm that has ruptured into the right side of the heart or pulmonary artery, coronary arteriovenous fistulas, and an aberrant left coronary artery with massive collaterals from the right coronary display dynamics similar to that of a PDA with a continuous murmur and a wide pulse pressure. Truncus arteriosus with torrential pulmonary flow also has an aortic runoff physiology. A peripheral arteriovenous fistula also results in a wide pulse pressure, but the distinctive precordial murmur of a PDA is not
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PROGNOSIS AND COMPLICATIONS

Spontaneous closure of the ductus after infancy is extremely rare. Patients with a small PDA may live a normal span with few or no cardiac symptoms, but late manifestations may occur. In patients with a large PDA, cardiac failure most often occurs in early infancy but may occur later in life, even with a moderate-sized communication.

Infective endarteritis may be seen at any age. Pulmonary or systemic emboli may occur. Rare complications include aneurysmal dilation of the pulmonary artery or the ductus, calcification of the ductus, noninfective thrombosis of the ductus with embolization, and paradoxical emboli. Pulmonary hypertension (Eisenmenger syndrome) usually develops in patients with a large PDA who do not undergo ductal closure (see Chapter 433.2).

TREATMENT

Irrespective of age, patients with PDA require catheter or surgical closure. In patients with a small PDA, the rationale for closure is prevention of bacterial endarteritis or other late complications. In patients with a moderate to large PDA, closure is accomplished to treat heart failure or prevent the development of pulmonary vascular disease, or both. Once the diagnosis of a moderate to large PDA is made, treatment should not be unduly postponed after adequate medical therapy for cardiac failure has been instituted.

Transcatheter PDA closure is routinely performed in the cardiac catheterization laboratory (Fig. 426-11). Small PDAs are generally closed with intravascular coils. Moderate to large PDAs may be closed with an umbrella-like device or with a catheter-introduced sac into which several coils are released. Surgical closure of a PDA can be accomplished by a standard left thoracotomy or using thoracoscopic minimally invasive techniques. Because the case fatality rate with interventional or surgical treatment is considerably less than 1% and the risk without it is greater, closure of the ductus is indicated in asymptomatic patients, preferably before 1 yr of age. Pulmonary hypertension is not a contraindication to surgery at any age if it can be demonstrated at cardiac catheterization that the shunt flow is still predominantly left to right and that severe pulmonary vascular disease is not present. After closure, symptoms of cardiac failure rapidly disappear. Infants who had failed to thrive usually have immediate improvement in physical development. The pulse and blood pressure return to normal, and the machinery-like murmur disappears. A functional systolic murmur over the pulmonary area may persist; it may represent turbulence in a persistently dilated pulmonary artery. The radiographic signs of cardiac enlargement and pulmonary overcirculation disappear over a period of several months, and the electrocardiogram becomes normal.

Figure 426-10  Echocardiogram in a newborn with a small- to moderate-size patent ductus arteriosus. A, Color Doppler performed in a parasternal short axis view shows flow (arrow) from the aorta into the main pulmonary artery. B, Doppler evaluation demonstrates retrograde diastolic flow into the pulmonary artery. AV, aortic valve; DescAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle.

Figure 426-11  Transcatheter closure of a small patent ductus arteriosus using a coil. A, Angiogram of transverse and descending aorta shows small PDA (arrow). B, Coil (arrow) has been extruded from sheath and is being positioned in ductal lumen. C, Angiogram demonstrating total occlusion of PDA by coil (arrow). DescAo, descending aorta; LSCA, left subclavian artery.
PATENT DUCTUS ARTERIOSUS IN LOW BIRTHWEIGHT INFANTS
See Chapter 101.

Bibliography is available at Expert Consult.

426.9 Aortopulmonary Window Defect
Daniel Bernstein

An aortopulmonary window defect consists of a communication between the ascending aorta and the main pulmonary artery. The presence of pulmonary and aortic valves and an intact ventricular septum distinguishes this anomaly from truncus arteriosus (see Chapter 431.8). Symptoms of heart failure appear during early infancy; occasionally, minimal cyanosis is present. The defect is usually large, and the cardiac murmur is usually systolic with an apical mid-diastolic rumble as a result of the increased blood flow across the mitral valve. In the rare instance when the communication is smaller and pulmonary hypertension is absent, the findings on examination can mimic those of a PDA (wide pulse pressure and a continuous murmur at the upper sternal borders). The electrocardiogram shows either left ventricular or biventricular hypertrophy. Radiographic studies demonstrate cardiac enlargement and prominence of the pulmonary artery and intrapulmonary vasculature. The echocardiogram shows enlarged left-sided heart chambers; the window defect can best be delineated with color flow Doppler. CT or MRI angiography can also be used to visualize the defect (see Fig. 423-26 in Chapter 423).

Cardiac catheterization, usually performed in older children to evaluate pulmonary vascular resistance, reveals a left-to-right shunt at the level of the pulmonary artery, as well as hyperkinetic pulmonary hypertension, because the defect is almost always large. Selective aortography with injection of contrast medium into the ascending aorta demonstrates the lesion, and manipulation of the catheter from the main pulmonary artery directly to the ascending aorta is also diagnostic.

An aortopulmonary window defect is surgically corrected during infancy. If surgery is not carried out in infancy, survivors carry the risk of progressive pulmonary vascular obstructive disease, similar to that of other patients who have large intracardiac or great vessel communications.

426.10 Coronary Artery Fistula
Daniel Bernstein

A congenital fistula may exist between a coronary artery and an atrium, ventricle (especially the right), or pulmonary artery. Sometimes, multiple fistulas exist. Regardless of the recipient chamber, the clinical signs are similar to those of PDA, although the machinery-like murmur may be more diffuse. If the flow is substantial, the involved coronary artery may be dilated or aneurysmal. The anatomic abnormality is usually demonstrable by color flow Doppler echocardiography and, during catheterization, by injection of contrast medium into the ascending aorta. Small fistulas may be hemodynamically insignificant and may even close spontaneously. If the shunt is large, treatment consists of either transcatheter coil embolization or, for lesions not amenable to catheter intervention, surgical closure of the fistula.

426.11 Ruptured Sinus of Valsalva Aneurysm
Daniel Bernstein

When 1 of the sinuses of Valsalva of the aorta is weakened by congenital or acquired disease, an aneurysm may form and eventually rupture,
Bibliography
Chapter 427
Acyanotic Congenital Heart Disease: Obstructive Lesions

427.1 Pulmonary Valve Stenosis with Intact Ventricular Septum
Daniel Bernstein

Of the various forms of right ventricular outflow obstruction with an intact ventricular septum, the most common is isolated valvular pulmonary stenosis, which accounts for 7-10% of all congenital heart defects. The valve cusps are deformed to various degrees and, as a result, the valve opens incompletely during systole. The valve may be bicuspid or tricuspid and the leaflets partially fused together with an eccentric outlet. This fusion may be so severe that only a pinhole central opening remains. If the valve is not severely thickened, it produces a dome-like obstruction to right ventricular outflow during systole. Isolated infundibular or subvalvular stenosis, supravalvular pulmonary stenosis, and branch pulmonary artery stenosis are also encountered. In cases where pulmonary valve stenosis is associated with a ventricular septal defect (VSD) but without anterior deviation of the infundibular septum and overriding aorta, this condition is better classified as pulmonary stenosis with VSD rather than as tetralogy of Fallot (see Chapter 430.1). Pulmonary stenosis and an atrial septal defect (ASD) are also occasionally seen as associated defects. The clinical and laboratory findings reflect the dominant lesion, but it is important to rule out any associated anomalies. Pulmonary stenosis as a result of valve dysplasia is the most common cardiac abnormality in Noonan syndrome (see Chapter 81), and is associated, in approximately 50% of cases, with a mutation in the gene PTPN11, encoding the protein tyrosine phosphatase SHP-2 on chromosome 12. The mechanism for pulmonic stenosis is unknown, although maldevelopment of the distal portion of the bulbus cordis and the sequelae of fetal endocarditis have been suggested as etiologies. Pulmonary stenosis can also be a component of LEOPARD syndrome (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness syndrome), often associated with hypertrophic cardiomyopathy. Mutations in the genes PTPN11, RAF1 and BRAF have been implicated in LEOPARD syndrome. Pulmonary stenosis, either of the valve or the branch pulmonary arteries, is a common finding in patients with arteriohepatic dysplasia, also known as Alagille syndrome (see Chapter 356). In this syndrome and in some patients with isolated pulmonic stenosis, a mutation is present in the jagged1 gene.
Part XX

**PATHOPHYSIOLOGY**

The obstruction to outflow from the right ventricle to the pulmonary artery results in increased right ventricular systolic pressure and wall stress, which leads to hypertrophy of the right ventricle (Fig. 427-1). The severity of these abnormalities depends on the size of the restricted valve opening. In severe cases, right ventricular pressure may be higher than systemic arterial systolic pressure, whereas with milder obstruction, right ventricular pressure is only mildly or moderately elevated. Pulmonary artery pressure (distal to the obstruction) is normal or decreased. Arterial oxygen saturation will be normal even in cases of severe stenosis, unless an intracardiac communication such as a VSD or ASD is allowing blood to shunt from right to left. When severe pulmonic stenosis occurs in a neonate, decreased right ventricular compliance often leads to cyanosis as a result of right-to-left shunting through a foramen ovale, the patient’s systemic oxygen saturation will be normal.

**CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS**

Patients with mild or moderate stenosis usually do not have any symptoms. Growth and development are most often normal. If the stenosis is severe, signs of right ventricular failure such as hepatomegaly, peripheral edema, and exercise intolerance may be present. In a neonate or young infant with critical pulmonic stenosis, signs of right ventricular failure may be more prominent, and cyanosis is often present because of right-to-left shunting at the foramen ovale.

With mild pulmonary stenosis, venous pressure and pulse are normal. The heart is not enlarged, the apical impulse is normal, and the right ventricular impulse is not palpable. A sharp pulmonic ejection click immediately after the 1st heart sound is heard at the left upper sternal border during expiration. The 2nd heart sound is split, with a pulmonary component of normal intensity that may be slightly delayed. A relatively short, low- or medium-pitched systolic ejection murmur is maximally audible over the pulmonic area and radiates minimally to the lung fields bilaterally. The electrocardiogram is normal or characteristic of mild right ventricular hypertrophy; inversion of the T waves in the right precordial leads may be seen. Remember that the T wave in lead V1 should normally be inverted until at least 6-8 yr of age. Therefore, a positive T wave in V1 in a young child is a sign of right ventricular hypertrophy. The only abnormality demonstrable radiographically is usually poststenotic dilation of the pulmonary artery. Two-dimensional echocardiography shows right ventricular hypertrophy and a slightly thickened pulmonic valve, which domes in systole; Doppler studies demonstrate a right ventricle to pulmonary artery gradient of ≤30 mm Hg.

In moderate pulmonic stenosis, venous pressure may be slightly elevated; in older children, a prominent a wave may be noted in the jugular pulse. A right ventricular lift may be palpable at the lower left sternal border. The 2nd heart sound is split, with a delayed and soft pulmonary component. As valve motion becomes more limited with more severe degrees of stenosis, both the pulmonic ejection click and the pulmonic 2nd sound may become inaudible. With increasing degrees of stenosis, the peak of the systolic ejection murmur is prolonged later into systole, and its quality becomes louder and harsher (higher frequency). The murmur radiates more prominently to both lung fields.

The electrocardiogram reveals right ventricular hypertrophy, sometimes with a prominent spiked P wave. Radiographically, the heart can vary from normal size to mildly enlarged with uplifting of the apex because of the prominence of the right ventricle; pulmonary vascularity may be normal or slightly decreased. The echocardiogram shows a thickened pulmonic valve with restricted systolic motion. Doppler examination demonstrates a right ventricle to pulmonary artery pressure gradient in the 30-60 mm Hg range. Mild tricuspid regurgitation may be present and allows Doppler confirmation of right ventricular systolic pressure.

In severe stenosis, mild to moderate cyanosis may be noted in patients with an interatrial communication (ASD or patent foramen ovale). In the absence of any intracardiac shunt, cyanosis is absent. If hepatic enlargement and peripheral edema are present, they are an indication of right ventricular failure. Elevation of venous pressure is common and is caused by a large presystolic jugular a wave. The heart is moderately or greatly enlarged, and a conspicuous parasternal right ventricular lift is present and frequently extends to the left midclavicular line. The pulmonary component of the 2nd sound is usually inaudible. A loud, long, and harsh systolic ejection murmur, usually accompanied by a thrill, is maximally audible in the pulmonic area and may radiate over the entire precordium, to both lung fields, into the neck, and to the back. The peak of the murmur occurs later in systole, as valve opening becomes more restricted. The murmur frequently encompasses the aortic component of the 2nd sound but is not preceded by an ejection click.

The electrocardiogram shows gross right ventricular hypertrophy, frequently accompanied by a tall, spiked P wave. Radiographic studies confirm the presence of cardiac enlargement with prominence of the right ventricle and right atrium. Prominence of the main pulmonary artery segment may be seen due to poststenotic dilation (Fig. 427-2). Intrapulmonary vascularity is decreased. The 2-dimensional echocardiogram shows severe deformity of the pulmonary valve and right ventricular hypertrophy (Fig. 427-3). In the late stages of the disease, systolic dysfunction of the right ventricle may be seen, and in these cases the ventricle may become dilated, with prominent tricuspid regurgitation. Doppler studies demonstrate a high gradient (>60 mm Hg) across the pulmonary valve. The classic findings of severe pulmonary stenosis in older children are rarely seen because of early intervention. Signs of critical pulmonic stenosis, with all of the features of severe pulmonic stenosis plus cyanosis, are usually encountered in the neonatal period.

Cardiac catheterization is not generally required for diagnostic purposes but is undertaken as part of a balloon valvuloplasty procedure. Catheterization demonstrates an abrupt pressure gradient across the
Acyanotic Congenital Heart Disease: Obstructive Lesions

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Figure 427-2. X-ray of a patient with valvular pulmonary stenosis and a normal aortic root. The heart size is within normal limits, but post-stenotic dilation of the pulmonary artery is present.

Figure 427-3. Echocardiogram demonstrating valvar pulmonary stenosis. A, Subcostal view showing thickened pulmonary valve leaflets (between crosshatches). B, Doppler study indicating a 95 mm Hg peak pressure gradient across the stenotic valve. MPA, main pulmonary artery; RV, right ventricle.

Figure 427-4. Valvar pulmonary stenosis and balloon valvuloplasty. A, Right ventricular angiogram showing severely stenotic pulmonary valve with narrow jet of blood flowing across. B, Inflation of the balloon catheter showing the indentation (arrow) made on the balloon from the stenotic valve. (Photos courtesy of Dr. Jeffrey Feinstein, Stanford University, Stanford, CA.)

Cases. If cardiac output is low or a significant right-to-left shunt exists across the atrial septum, the pressure gradient may underestimate the degree of valve stenosis. Selective right ventriculography demonstrates the thickened, poorly mobile valve. In mild to moderate stenosis, doming of the valve in systole is readily seen. Flow of contrast medium through the stenotic valve in ventricular systole produces a narrow jet of dye that fills the dilated main pulmonary artery. Subvalvar hypertrophy that may intensify the obstruction may be present.

TREATMENT

Patients with moderate or severe isolated pulmonary stenosis require relief of the obstruction. Balloon valvuloplasty is the initial treatment of choice for the majority of patients (Fig. 427-4). Patients with severely thickened pulmonic valves, especially common in those with Noonan syndrome, may require surgical intervention. In a neonate with critical pulmonic stenosis, urgent treatment by either balloon valvuloplasty or surgical valvotomy is warranted.

Excellent results are obtained in most instances. The gradient across the pulmonary valve is markedly reduced or abolished. In the early period after balloon valvuloplasty, a small to moderate residual gradient may remain because of muscular infundibular narrowing; it usually resolves with time. A short, early decrescendo diastolic murmur may be heard at the mid to upper left sternal border as a result of pulmonary valvular insufficiency. The degree of insufficiency is not usually clinically significant. No difference in patient status after valvuloplasty or surgery is noted at late follow-up; recurrence is unusual after successful treatment except in those patients with extremely dysplastic valves. In the small minority of patients where the degree of pulmonary regurgitation is more severe, right ventricular dilation may ensue, and these patients require careful follow-up and may require surgical intervention.
PROGNOSIS AND COMPLICATIONS

Heart failure occurs only in severe cases and most often during the 1st mo of life. The development of cyanosis from a right-to-left shunt across a foramen ovale is almost exclusively seen in the neonatal period when the stenosis is severe. Infective endocarditis is a risk, but is not common in childhood.

Children with mild stenosis can lead a normal life, but their progress should be evaluated at regular intervals. Patients who have small gradients rarely show progression and do not need intervention, but a significant gradient is more likely to develop in children with moderate stenosis as they grow older. Worsening of obstruction may also be due to the development of secondary subvalvular muscular and fibrous tissue hypertrophy. In untreated severe stenosis, the course may abruptly worsen with the development of right ventricular dysfunction and cardiac failure. Infants with critical pulmonic stenosis require urgent catheter balloon valvuloplasty or surgical valvotomy. Development of right ventricular failure many years after pulmonary balloon valvuloplasty is uncommon. Nonetheless, patients should be followed serially for worsening pulmonary insufficiency and right ventricular dilation.

Bibliography is available at Expert Consult.

427.2 Infundibular Pulmonary Stenosis andDouble-Chamber Right Ventricle

Daniel Bernstein

Infundibular pulmonary stenosis is caused by muscular or fibrous obstruction in the outflow tract of the right ventricle. The site of obstruction may be close to the pulmonary valve or well below it; an infundibular chamber may be present between the right ventricular cavity and the pulmonary valve. In many cases, a VSD may have been present initially and later closed spontaneously. When the pulmonary valve is also stenotic, the combined defect is primarily classified as valvular stenosis with secondary infundibular hypertrophy. The hemodynamics and clinical manifestations of patients with isolated infundibular pulmonary stenosis are similar, for the most part, to those described in the discussion of isolated valvular pulmonary stenosis (see Chapter 427.1).

A common variation in right ventricular outflow obstruction below the pulmonary valve is that of a double-chambered right ventricle. In this condition, a muscular band is present in the mid-right ventricular region; the band divides the chamber into 2 parts and creates obstruction between the inlet and outlet portions. An associated VSD that may close spontaneously is often noted. Obstruction is not usually seen early in life but may progress rapidly in a similar manner to the progressive infundibular obstruction observed with tetralogy of Fallot (see Chapter 430.1).

The diagnosis of isolated right ventricular infundibular stenosis or double-chambered right ventricle is usually made by echocardiography. The ventricular septum must be evaluated carefully to determine whether an associated VSD is present. The prognosis for untreated cases of severe right ventricular outflow obstruction is similar to that for valvular pulmonary stenosis. When the obstruction is moderate to severe, surgery is indicated. After surgery, the pressure gradient is abolished or markedly reduced and the long-term outlook is excellent.

427.3 Pulmonary Stenosis in Combination with an Intracardiac Shunt

Daniel Bernstein

Valvular or infundibular pulmonary stenosis, or both, may be associated with either an ASD or a VSD. In these patients, the clinical features depend on the degree of pulmonary stenosis, which determines whether the net shunt is from left to right or from right to left.

The presence of a large left-to-right shunt at the atrial or ventricular level is evidence that the pulmonary stenosis is mild. These patients have symptoms similar to those of patients with an isolated ASD or VSD. With increasing age, worsening of the obstruction may limit the shunt and result in a gradual improvement in symptoms. Eventually, particularly in patients with pulmonary stenosis and VSD, a further increase in obstruction may lead to right-to-left shunting and cyanosis. When a patient with a VSD has evidence of decreasing heart failure and increased right ventricular forces on the electrocardiogram, one must differentiate between the development of increasing pulmonary stenosis versus the onset of pulmonary vascular disease (Eisenmenger syndrome, Chapter 433.2).

These anomalies are readily repaired surgically. Defects in the atrial or ventricular septum are closed, and the pulmonary stenosis is relieved by resection of infundibular muscle or pulmonary valvotomy, or both, as indicated. Patients with a predominant right-to-left shunt have symptoms similar to those of patients with tetralogy of Fallot (see Chapter 430.1).

427.4 Peripheral Pulmonary Stenosis

Daniel Bernstein

Single or multiple constrictions may occur anywhere along the major branches of the pulmonary arteries and may range from mild to severe and from localized to extensive. Frequently, these defects are associated with other types of congenital heart disease, including valvular pulmonic stenosis, tetralogy of Fallot, patent ductus arteriosus (PDA), VSD, ASD, and supravalvular aortic stenosis. A familial tendency has been recognized in some patients with peripheral pulmonic stenosis. A high incidence is found in infants with congenital rubella syndrome. The combination of supravalvular aortic stenosis with pulmonary arterial branch stenosis, idiopathic hypercalcemia of infancy, elfin facies, and mental retardation is known as Williams syndrome, a condition associated with deletion of the elastin gene in region 7q11.23 on chromosome 7. Peripheral pulmonary stenosis is also associated with the Alagille syndrome, which may be associated with a mutation in the Jagged1 gene.

A mild constriction has little effect on the pulmonary circulation. With multiple severe constrictions, pressure is increased in the right ventricle and in the pulmonary artery proximal to the site of obstruction. When the anomaly is isolated, the diagnosis is suspected by the presence of murmurs in widespread locations over the chest, either anteriorly or posteriorly. These murmurs are usually systolic ejection in quality but may be continuous. Most often, the physical signs are dominated by the associated anomaly, such as tetralogy of Fallot (see Chapter 430.1).

In the immediate newborn period, a mild and transient form of peripheral pulmonic stenosis may be present. Physical findings are generally limited to a soft systolic ejection murmur, which can be heard over either or both lung fields. It is the absence of other physical findings of valvular pulmonic stenosis (right ventricular lift, soft pulmonic 2nd sound, systolic ejection click, murmur loudest at the upper left sternal border) that supports this diagnosis. This murmur usually disappears by 1-2 mo.

If the stenosis is severe, the electrocardiogram shows evidence of right ventricular and right atrial hypertrophy, and the chest radiograph shows cardiomegaly and prominence of the main pulmonary artery. The pulmonary vasculature is usually normal; in some cases, however, small intrapulmonary vascular shadows are seen that represent areas of poststenotic dilation. Echocardiography is limited in its ability to visualize the distal branch pulmonary arteries. Doppler examination demonstrates the acceleration of blood flow through the stenoses and, if tricuspid regurgitation is present, allows an estimation of right ventricular systolic pressure. MRI and CT are extremely helpful in delineating distal obstructions; if moderate to severe disease is suspected, the diagnosis is usually confirmed by cardiac catheterization.


Severe obstruction of the main pulmonary artery and its primary branches can be relieved during corrective surgery for associated lesions such as the tetralogy of Fallot or valvar pulmonary stenosis. If peripheral pulmonic stenosis is isolated, it may be treated by catheter balloon dilation, sometimes with placement of an intravascular stent (see Fig. 423-29 in Chapter 423).

### 427.5 Aortic Stenosis

**Daniel Bernstein**

#### PATHOPHYSIOLOGY

Congenital aortic stenosis accounts for ≈5% of cardiac malformations recognized in childhood; a bicuspid aortic valve, one of the most common congenital heart lesions overall, is identified in up to 1.5% of adults and may be asymptomatic in childhood. Aortic stenosis is more frequent in males (3:1). There are families with multiple individuals affected with bicuspid aortic valve, and several genes have been implicated, including NOTCH1 on chromosome 9q34.3.

In the most common form, valvular aortic stenosis, the leaflets are thickened and the commissures are fused to varying degrees. Left ventricular systolic pressure is increased as a result of the obstruction to outflow. The left ventricular wall hypertrophies in compensation; as its compliance decreases, end-diastolic pressure increases as well.

**Subvalvular (subaortic) stenosis** with a discrete fibromuscular shelf below the aortic valve is also an important form of left ventricular outflow tract obstruction. This lesion is frequently associated with other forms of congenital heart disease such as mitral stenosis and coarctation of the aorta (Shone syndrome) and may progress rapidly in severity. It is less commonly diagnosed during early infancy and may develop despite previous documentation of no left ventricular outflow tract obstruction. Subvalvular aortic stenosis may become apparent after successful surgery for other congenital heart defects (coarctation of the aorta, PDA, VSD), may develop in association with mild lesions that have not been surgically repaired, or may occur as an isolated abnormality. Subvalvular aortic stenosis may also be caused by a markedly hypertrophied ventricular septum in association with hypertrophic cardiomyopathy (see Chapter 439.2).  

**Supravalvular aortic stenosis**, the least-common type, may be sporadic, familial, or associated with Williams syndrome, which includes mental retardation (IQ range: 41-80), elfin facies (full face, broad forehead, flattened bridge of the nose, long upper lip, and rounded cheeks) (Fig. 427-5), and idiopathic hypercalcemia of infancy. Additional features include loquacious personality, hypersensitivity to sound, spasticity, hypoplastic nails, dental anomalies (partial anodontia, microdontia enamel hypoplasia), joint hypermobility, nephrocalcinosis, hypothyroidism, and poor weight gain. Narrowing of the coronary artery ostia can occur in patients with supravalvar aortic stenosis and should be carefully evaluated. Stenosis of other arteries, in particular, the branch pulmonary arteries, may also be present. Williams syndrome has been shown to be due to a deletion involving the elastin gene on chromosome 7q1.23.

#### CLINICAL MANIFESTATIONS

Symptoms in patients with aortic stenosis depend on the severity of the obstruction. Severe aortic stenosis that occurs in early infancy is termed critical aortic stenosis and is associated with left ventricular failure and signs of low cardiac output. Heart failure, cardiomegaly, and pulmonary edema are severe, the pulses are weak in all extremities, and the skin may be pale or grayish. Urine output may be diminished. If cardiac output is significantly decreased, the intensity of the murmur at the right upper sternal border may be minimal. Most children with less-severe forms of aortic stenosis remain asymptomatic and display normal growth and development. The murmur is usually discovered during routine physical examination. Rarely, fatigue, angina, dizziness, or syncope may develop in an older child with previously undiagnosed severe obstruction to left ventricular outflow. Sudden death has been reported with aortic stenosis but usually occurs in patients with severe left ventricular outflow obstruction in whom surgical relief has been delayed.

The physical findings are dependent on the degree of obstruction to left ventricular outflow. In mild stenosis, the pulses, heart size, and apical impulse are all normal. With increasing degrees of severity, the pulses become diminished in intensity and the heart may be enlarged, with a left ventricular apical thrust. Mild to moderate valvular aortic stenosis is usually associated with an early systolic ejection click, best heard at the apex and left sternal edge. Unlike the click in pulmonic stenosis, its intensity does not vary with respiration. Clicks are unusual in more-severe aortic stenosis or in discrete subaortic stenosis. If the stenosis is severe, the 1st heart sound may be diminished because of decreased compliance of the thickened left ventricle. Normal splitting of the 2nd heart sound is present in mild to moderate obstruction. In patients with severe obstruction, the intensity of aortic valve closure is diminished, and, rarely in children, the 2nd sound may be split paradoxically (becoming wider in expiration). A 4th heart sound may be audible when the obstruction is severe as a result of decreased left ventricular compliance.

The intensity, pitch, and duration of the systolic ejection murmur are other indications of severity. The louder, harsher (higher pitch), and longer the murmur, the greater the degree of obstruction is. The typical murmur is audible maximally at the right upper sternal border and radiates to the neck and the left midsternal border. It is usually accompanied by a thrill in the suprasternal notch. In patients with subvalvular aortic stenosis, the murmur may be maximal along the left sternal border or even at the apex. A soft decrescendo diastolic murmur indicative of aortic insufficiency is often present when the obstruction is subvalvular or in patients with a bicuspid aortic valve. Occasionally, an apical short mid-diastolic rumbling murmur is audible; this murmur should raise suspicion of associated mitral valve stenosis.
LABORATORY FINDINGS AND DIAGNOSIS

The diagnosis can usually be made on the basis of the physical examination and the severity of obstruction confirmed by laboratory tests. If the pressure gradient across the aortic valve is mild, the electrocardiogram is likely to be normal. The electrocardiogram may occasionally be normal even with more severe obstruction, but evidence of left ventricular hypertrophy and strain (inverted T waves in the left precordial leads) is generally present if severe stenosis is long-standing. The chest radiograph frequently shows a prominent ascending aorta, but the aortic knob is normal. Heart size is typically normal. Valvular calcification has been noted only in older children and adults. Echocardiography identifies both the site and the severity of the obstruction. Two-dimensional imaging shows left ventricular hypertrophy and the thickened and domed aortic valve (Fig. 427-6). The echo will also demonstrate the number of valve leaflets and their morphology, and the presence of a subaortic membrane or supravalvar stenosis. Associated anomalies of the mitral valve or aortic arch or a VSD or PDA are present in up to 20% of cases. In the absence of left ventricular failure, the shortening fraction of the left ventricle may be increased because the ventricle is hypercontractile. In infants with critical aortic stenosis, the left ventricular shortening fraction is usually decreased and may be quite poor. The endocardium may appear bright, indicative of the development of endocardial fibrous scarring, known as endocardial fibroelastosis. Doppler studies show the specific site of obstruction and determine the peak and mean systolic left ventricular outflow tract gradients. When severe aortic obstruction is associated with left ventricular dysfunction, the Doppler-derived valve gradient may markedly underestimate the severity of the obstruction because of the low cardiac output across the valve.

Left-heart catheterization, usually performed in conjunction with aortic balloon valvuloplasty, demonstrates the magnitude of the pressure gradient from the left ventricle to the aorta. The aortic pressure curve is abnormal if the obstruction is severe. In patients with severe obstruction and decreased left ventricular compliance, left atrial pressure is increased and pulmonary hypertension may be present. When a critically ill infant with left ventricular outflow tract obstruction undergoes cardiac catheterization, left ventricular function is often markedly decreased. As with the echocardiogram, the gradient measured across the stenotic aortic valve may underestimate the degree of obstruction because of low cardiac output. Actual measurement of cardiac output by thermodilution and calculation of the aortic valve area may be helpful.

TREATMENT

Balloon valvuloplasty is indicated for children with moderate to severe valvular aortic stenosis to prevent progressive left ventricular dysfunction and the risk of syncope and sudden death. Valvuloplasty should be advised when the peak-to-peak systolic gradient between the left ventricle and aorta exceeds 60-70 mm Hg at rest, assuming normal cardiac output, or for lesser gradients when symptoms or electrocardiographic changes are present. For more rapidly progressive subaortic obstructive lesions, a gradient of 40-50 mm Hg or the presence of aortic insufficiency is considered an indication for surgery. Balloon valvuloplasty is the procedure of choice even in the neonatal period. Surgical treatment is usually reserved for extremely dysplastic aortic valves that are not amenable to balloon therapy or in patients who also have subvalvar or valvar (also known as supravalvar) stenosis.

Discrete subaortic stenosis can be resected without damage to the aortic valve, the anterior leaflet of the mitral valve, or the conduction system. This type of obstruction is not usually amenable to catheter treatment. Relief of supravalvular stenosis is also achieved surgically, and the results are excellent if the area of obstruction is discrete and not associated with a hypoplastic aorta. In association with supravalvular aortic stenosis, one or both coronary arteries may be stenotic at their origins because of a thick supra-aortic fibrous ridge. For patients who have aortic stenosis in association with severe tunnel-like subaortic obstruction, the left ventricular outflow tract can be enlarged by “borrowing” space anteriorly from the right ventricular outflow tract (the Konno procedure).

Regardless of whether surgical or catheter treatment has been carried out, aortic insufficiency or calcification with re-stenosis is likely to occur years or even decades later and eventually require reoperation and often aortic valve replacement. When recurrence develops, it may not be associated with early symptoms. Signs of recurrent stenosis include electrocardiographic signs of left ventricular hypertrophy, an increase in the Doppler echocardiographic gradient, deterioration in echocardiographic indices of left ventricular function, and recurrence of signs or symptoms during graded treadmill exercise. Evidence of significant aortic regurgitation includes symptoms of heart failure, cardiac enlargement on roentgenogram, and left ventricular dilation on echocardiogram. The choice of reparative procedure depends on the relative degree of stenosis and regurgitation.

When aortic valve replacement is necessary, the choice of procedure often depends on the age of the patient. Homograft valves tend to calcify more rapidly in younger children, but they do not require chronic anticoagulation. Mechanical prosthetic valves are much longer lasting, yet they require anticoagulation, which can be difficult to manage in young children. In adolescent girls who are nearing child-bearing age, consideration of the teratogenic effects of warfarin may warrant the use of a homograft valve. None of these options are perfect for a younger child who requires valve replacement because neither homograft nor mechanical valves grow with the patient. An alternative operation is aortopulmonary translocation (Ross procedure); it involves removing the patient’s own pulmonary valve and using it to replace the abnormal aortic valve. A homograft is then placed in the pulmonary position. The potential advantage of this procedure is the possibility for growth of the translocated living “neoaortic” valve and the increased longevity of the homograft valve when placed in the lower pressure pulmonary circulation. The long-term success of this operation, especially in young children, is still being investigated. Transcatheter stent valves, which are tissue valves sewn into the inside.
of an expandable metal stent, are currently in clinical trials in adults, mainly in those who are not good candidates for standard surgical replacement. These can be implanted in the cardiac catheterization laboratory using a percutaneous approach. Tissue-engineered replacement valves grown in the laboratory from the patient's own arterial endothelial cells are another prospect for long-term palliation and are currently under development in animal models.

**PROGNOSIS**

Neonates with critical aortic stenosis may have severe heart failure and deteriorate rapidly to a low-output shock state. Emergency surgery or balloon valvuloplasty is lifesaving, but the mortality risk is not trivial. Neonates who die of critical aortic stenosis frequently have significant left ventricular endocardial fibroelastosis. Those who survive may develop signs of left ventricular diastolic muscle dysfunction (restrictive cardiomyopathy) and require cardiac transplantation (see Chapter 443).

In older infants and children with mild to moderate aortic stenosis, the prognosis is reasonably good, although disease progression over a period of 5-10 yr is common. Patients with aortic valve gradients <40-50 mm Hg are considered to have mild disease; those with gradients of 40-70 mm Hg have moderate disease. These patients usually respond well to treatment (either surgery or valvuloplasty), although reoperations on the aortic valve are often required later in childhood or in adult life, and many patients eventually require valve replacement. In unoperated patients with severe obstruction, sudden death is a significant risk and often occurs during or immediately after exercise. Aortic stenosis is one of the causes of sudden cardiac death in the pediatric age group.

Patients with moderate to severe degrees of aortic stenosis should not participate in active competitive sports. In those with milder disease, sports participation is less severely restricted. The status of each patient should be reviewed at least annually and intervention advised if progression of signs or symptoms occurs. Prophylaxis against infective endocarditis is no longer recommended unless a prosthetic valve has been inserted.

Older children and adults with isolated bicuspid aortic valve are at increased risk for developing dilation of their ascending aorta, even in the absence of significant stenosis. This risk increases with age, and the rate of increase is greatest in those with the largest aortic roots. In children, this dilation is usually mild and remains stable over many years of observation, but in older patients the aorta can dilate substantially and progressively. Whether these patients have some undiagnosed form of connective tissue disorder remains to be determined (as this form of dilation is similar to that seen in Marfan syndrome). Patients with Turner syndrome and bicuspid aortic valve do have an increased risk of aortic dilation. Although dissection and rupture are described complications of severe aortic root dilation in adults, there is not yet sufficient data to determine these risks in children. Only isolated cases have been reported.

Bibliography is available at Expert Consult.

### 427.6 Coarctation of the Aorta

*Daniel Bernstein*

Constrictions of the aorta of varying degrees may occur at any point from the transverse arch to the iliac bifurcation, but 98% occur just below the origin of the left subclavian artery at the origin of the ductus arteriosus (juxtaductal coarctation). The anomaly occurs twice as often in males as in females. Coarctation of the aorta may be a feature of **Turner syndrome** (see Chapters 81 and 586.1) and is associated with a bicuspid aortic valve in more than 70% of patients. Mitral valve abnormalities (a supraavalvar mitral ring or parachute mitral valve) and subaortic stenosis are potential associated lesions. When this group of left-sided obstructive lesions occurs together, they are referred to as the **Shone complex**.

**PATHOPHYSIOLOGY**

Coarctation of the aorta can occur as a discrete juxtaductal obstruction or as tubular hypoplasia of the transverse aorta starting at one of the head or neck vessels and extending to the ductal area (previously referred to as **preductal or infantile-type coarctation**; Fig. 427-7). Often, both components are present. It is postulated that coarctation may be initiated in fetal life by the presence of a cardiac abnormality that results in decreased blood flow anterograde through the aortic valve (e.g., bicuspid aortic valve, VSD). Alternatively, coarctation may be caused by abnormal extension of contractile ductal tissue into the aortic wall.

In patients with discrete juxtaductal coarctation, ascending aortic blood flows through the narrowed segment to reach the descending aorta, although left ventricular hypertension and hypertrophy result. In the 1st few days of life, the PDA may serve to widen the juxtaductal area of the aorta and provide temporary relief from the obstruction. Net left-to-right ductal shunting occurs in these acyanotic infants. With more-severe juxtaductal coarctation or in the presence of transverse arch hypoplasia, right ventricular blood is ejected through the ductus to supply the descending aorta. Perfusion of the lower part of the body is then dependent on right ventricular output (see Fig. 427-7). In this situation, the femoral pulses are palpable, and differential blood pressures may not be helpful in making the diagnosis. The ductal right-to-left shunting is manifested as differential cyanosis, with the upper extremities being pink and the lower extremities blue.

Such infants may have severe pulmonary hypertension and high pulmonary vascular resistance. Signs of heart failure are prominent. Occasionally, severely hypoplastic segments of the aortic isthmus may become completely atretic and result in an interrupted aortic arch, with the left subclavian artery arising either proximal or distal to the interruption. Coarctation associated with arch hypoplasia was once referred to as infantile type because its severity usually led to recognition of the
Bibliography


condition in early infancy. Adult type referred to isolated juxta-ductal coarctation, which, if mild, was not usually recognized until later childhood. These terms have been replaced with the more accurate anatomic terms describing the location and severity of the defect.

Blood pressure is elevated in the vessels that arise proximal to the coarctation; blood pressure as well as pulse pressure is lower below the constriction. The hypertension is not caused by the mechanical obstruction alone, but also involves neurohumoral mechanisms. Unless operated on in infancy, coarctation of the aorta usually results in the development of an extensive collateral circulation, chiefly from branches of the subclavian, superior intercostal, and internal mammary arteries, to create channels for arterial blood to bypass the area of coarctation. The vessels contributing to the collateral circulation may become markedly enlarged and tortuous by early adulthood.

CLINICAL MANIFESTATIONS

Coarctation of the aorta recognized after infancy is not usually associated with significant symptoms. Some children or adolescents complain about weakness or pain (or both) in the legs after exercise, but in many instances, even patients with severe coarctation are asymptomatic. Older children are frequently brought to the cardiologist’s attention when they are found to be hypertensive on routine physical examination.

The classic sign of coarctation of the aorta is a disparity in pulsation and blood pressure in the arms and legs. The femoral, popliteal, posterior tibial, and dorsalis pedis pulses are weak (or absent in up to 40% of patients), in contrast to the bounding pulses of the arms and carotid vessels. The radial and femoral pulses should always be palpated simultaneously for the presence of a radial-femoral delay. Normally, the femoral pulse occurs slightly before the radial pulse. A radial-femoral delay occurs when blood flow to the descending aorta is dependent on collaterals, in which case the femoral pulse is felt after the radial pulse. In normal persons (except neonates), systolic blood pressure in the legs obtained by the cuff method is 10-20 mm Hg higher than that in the arms. In coarctation of the aorta, blood pressure in the legs is lower than that in the arms; frequently, it is difficult to obtain. This differential in blood pressures is common in patients with coarctation who are older than 1yr, approximately 90% of whom have systolic hypertension in an upper extremity greater than the 95th percentile for age. It is important to determine the blood pressure in each arm; a pressure higher in the right than the left arm suggests involvement of the left subclavian artery in the area of coarctation. Occasionally, the right subclavian may arise anomalously from below the area of coarctation and result in a left arm pressure that is higher than the right. With exercise, a more prominent rise in systemic blood pressure occurs, and the upper-to-lower extremity pressure gradient will increase.

The precordial impulse and heart sounds are usually normal; the presence of a systolic ejection click or thrill in the suprasternal notch suggests a bicuspid aortic valve (present in 70% of cases). A short systolic murmur is often heard along the left sternal border at the 3rd and 4th intercostal spaces. The murmur is well transmitted to the left infrascapular area and occasionally to the neck. Often, the typical murmur of mild aortic stenosis can be heard in the 3rd right intercostal space. Occasionally, more significant degrees of obstruction are noted across the aortic valve. The presence of a low-pitched mid-diastolic murmur at the apex suggests mitral valve stenosis. In older patients with well-developed collateral blood flow, systolic or continuous murmurs may be heard over the left and right sides of the chest laterally and posteriorly. In these patients, a palpable thrill can occasionally be appreciated in the intercostal spaces on the back.

Neonates or infants with more severe coarctation, usually including some degree of transverse arch hypoplasia, initially have signs of lower body hypoperfusion, acidosis, and severe heart failure. These signs may be delayed days or weeks until after closure of the ductus arteriosus. If detected before ductal closure, patients may exhibit differential cyanosis, best demonstrated by simultaneous oximetry of the upper and lower extremities. On physical examination, the heart is large, and a systolic murmur is heard along the left sternal border with a loud 2nd heart sound.

DIAGNOSIS

Findings on roentgenographic examination depend on the age of the patient and on the effects of hypertension and the collateral circulation. Cardiac enlargement and pulmonary congestion are noted in infants with severe coarctation. During childhood, the findings are not striking until after the 1st decade, when the heart tends to be mildly or moderately enlarged because of left ventricular prominence. The enlarged left subclavian artery commonly produces a prominent shadow in the left superior mediastinum. Notching of the inferior border of the ribs from pressure erosion by enlarged collateral vessels is common by late childhood. In most instances, the descending aorta has an area of poststenotic dilation.

The electrocardiogram is usually normal in young children but reveals evidence of left ventricular hypertrophy in older patients. Neonates and young infants display right or biventricular hypertrophy. The segment of coarctation can generally be visualized by 2-dimensional echocardiography (Fig. 427-8); associated anomalies of the mitral and aortic valve can also be demonstrated. The descending aorta is hypopulsatile. Color Doppler is useful for demonstrating the specific site of the obstruction. Pulsed and continuous wave Doppler studies determine the pressure gradient directly at the area of coarctation; in the presence of a PDA, however, the severity of the narrowing may be underestimated. CT and MRI are valuable noninvasive tools for evaluation of coarctation when the echocardiogram is equivocal. Cardiac catheterization with selective left ventriculography and aortography is useful in occasional patients with additional anomalies and as a means of visualizing collateral blood flow. In cases that are well defined by echocardiography, CT, or MRI, diagnostic catheterization is not usually required before surgery.

Figure 427-8 Echocardiogram demonstrating coarctation of the aorta with hypoplastic transverse arch. A, Suprasternal notch shows marked narrowing beginning just distal to the brachiocephalic artery. B, Color Doppler demonstrates turbulent flow in the juxta ductal area (arrow). AscAo, ascending aorta; BR, brachiocephalic artery; LCA, left carotid artery; LSCA, left subclavian artery.
TREATMENT
In neonates with severe coarctation of the aorta, closure of the ductus often results in hypoperfusion, acidosis, and rapid deterioration. These patients should be given an infusion of prostaglandin E₁ to reopen the ductus and reestablish adequate lower extremity blood flow. Once a diagnosis has been confirmed and the patient stabilized, surgical repair should be performed. Older infants with heart failure but good perfusion should be managed with anticongestive measures to improve their clinical status before surgical intervention. There is usually no reason to delay surgical repair waiting for patient growth; successful repairs have been performed in small premature infants.

Older children with significant coarctation of the aorta should be treated relatively soon after diagnosis. Delay is unwarranted, especially after the 2nd decade of life, when the operation may be less successful because of decreased left ventricular function and degenerative changes in the aortic wall. Nevertheless, if cardiac reserve is sufficient, satisfactory repair is possible well into middle adulthood.

The procedure of choice for isolated juxtaductal coarctation of the aorta is controversial. Surgery remains the treatment of choice at most centers, and several surgical techniques are used. The area of coarctation can be excised and a primary re-anastomosis performed. Most often, the transverse aorta is splayed open and an "extended end-to-end" anastomosis performed to increase the effective cross-sectional area of the repair. The subclavian flap procedure, which involves division of the left subclavian artery and incorporation of it into the wall of the repaired coarctation has grown out of favor because of a higher degree of residual stenosis. Some centers favor a patch aortoplasty, in which the area of coarctation is enlarged with a roof of prosthetic material. The use of primary angioplasty for native coarctation remains controversial due to concern over subsequent recoarctation and aneurysm development. The use of primary stent placement is currently under evaluation in clinical trials and is most useful in conditions where surgical intervention may be associated with increased risk in patients with severe left ventricular dysfunction.

After surgery, a striking increase in the amplitude of pulsations in the lower extremities is noted. In the immediate postoperative course, "rebound" hypertension is common and requires medical management. This exaggerated acute hypertension gradually subsides and, in most patients, antihypertensive medications can be discontinued. Residual murmurs are common and may be the result of associated cardiac abnormalities, of a residual flow disturbance across the repaired area, or of collateral blood flow. Rare operative problems include spinal cord injury from aortic cross-clamping if the collaterals are poorly developed, chylothorax, diaphragm injury, and laryngeal nerve injury. If a left subclavian flap approach is used, the radial pulse and blood pressure in the left arm are diminished or absent.

POSTCOARCTECTOMY SYNDROME
Postoperative mesenteric arteritis may be associated with acute hypertension and abdominal pain in the immediate postoperative period. The pain varies in severity and may occur in conjunction with anorexia, nausea, vomiting, leukocytosis, intestinal hemorrhage, bowel necrosis, and small bowel obstruction. Relief is usually obtained with antihypertensive drugs (nitroprusside, esmolol, captopril) and intestinal decompression; surgical exploration is rarely required for bowel obstruction or infarction.

PROGNOSIS
Although restenosis in older patients after coarctectomy is rare, a significant number of infants operated on before 1 yr of age require revision later in childhood. All patients should be monitored carefully for the development of recoarctation and an aortic anastomotic aneurysm. Should recoarctation occur, balloon angioplasty is the procedure of choice. In these patients, scar tissue from previous surgery may make reoperation more difficult yet makes balloon angioplasty safer because of the lower incidence of aneurysm formation. Relief of obstruction with this technique is usually excellent. Intravascular stents are commonly used, especially in adolescents and young adults, with generally excellent results.

Repair of coarctation in the 2nd decade of life or beyond may be associated with a higher incidence of premature cardiovascular disease, even in the absence of residual cardiac abnormalities. Early onset of adult chronic hypertension may occur, even in patients with adequately resected coarctation.

Abnormalities of the aortic valve are present in most patients. Bicuspid aortic valves are common but do not generally produce clinical signs unless the stenosis is significant. The association of a PDA and coarctation of the aorta is also common. VSDs and ASDs may be suspected by signs of a left-to-right shunt; they are exacerbated by the increased resistance to flow through the left side of the heart. Mitral valve abnormalities are also occasionally seen, as is subvalvular aortic stenosis.

Severe neurologic damage or even death may rarely occur from associated cerebrovascular disease. Subarachnoid or intracerebral hemorrhage may result from rupture of congenital aneurysms in the circle of Willis, rupture of other vessels with destructive elastic and medial tissue, or rupture of normal vessels; these accidents are secondary to hypertension. Children with PHACE syndrome (posterior brain fossa anomalies, facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, eye anomalies syndrome) may have strokes (see Table 422-2 in Chapter 422). Abnormalities of the subclavian arteries may include involvement of the left subclavian artery in the area of coarctation, stenosis of the orifice of the left subclavian artery, and anomalous origin of the right subclavian artery.

Untreated, the great majority of older patients with coarctation of the aorta would succumb between the ages of 20 and 40 yr; some live well into middle life without serious disability. The common serious complications are related to systemic hypertension, which may result in premature coronary artery disease, heart failure, hypertensive encephalopathy, or intracranial hemorrhage. Heart failure may be worsened by associated anomalies. Infective endocarditis or endarteritis is a significant complication in adults. Aneurysms of the descending aorta or the enlarged collateral vessels may develop.

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427.7 Coarctation with Ventricular Septal Defect
Daniel Bernstein

Coarctation in the presence of a VSD results in both increased preload and afterload on the left ventricle, and patients with this combination of defects will be recognized either at birth or in the 1st mo of life and often have intractable cardiac failure. The magnitude of the left-to-right shunt through a VSD is dependent on the ratio of pulmonary to systemic vascular resistance. In the presence of coarctation, resistance to systemic outflow is enhanced by the obstruction, and the volume of the shunt is markedly increased. The clinical picture is that of a seriously ill infant with tachypnea, failure to thrive, and typical findings of heart failure. Often, the difference in blood pressure between the upper and lower extremities is not very marked because cardiac output may be low. Medical management should be used to stabilize the patient initially; however, it should not be used to delay corrective surgery inordinately.

In most cases, coarctation is the major anomaly causing the severe symptoms, and resection of the coarcted segment results in striking improvement. Many centers routinely repair both the VSD and coarctation at the same operation through a midline sternotomy using cardiopulmonary bypass. Some centers repair the coarctation through a left lateral thoracotomy and, at the same time, place a pulmonary artery band to decrease the ventricular-level shunt. This may be performed when a complicated VSD is present (multiple VSDs, apical muscular VSD), to avoid open heart surgery during infancy for these complex ventricular septal abnormalities.
Bibliography


427.8 Coarctation with Other Cardiac Anomalies and Interrupted Aortic Arch
Daniel Bernstein

Coarctation often occurs in infancy in association with other major cardiovascular anomalies, including hypoplastic left heart, severe mitral or aortic valve disease, transposition of the great arteries, and variations of double-outlet or single ventricle. The clinical manifestations depend on the effects of the associated malformations, as well as on the coarctation itself.

Coarctation of the aorta associated with severe mitral and aortic valve disease may have to be treated within the context of the hypoplastic left heart syndrome (see Chapter 431.10), even if the left ventricular chamber is not severely hypoplastic. Such patients usually have a long segment of narrow transverse aortic arch in addition to an isolated coarctation at the site of the ductus arteriosus. Coarctation of the aorta with transposition of the great arteries or single ventricle may be repaired alone or in combination with other corrective or palliative measures.

Complete interruption of the aortic arch is the most severe form of coarctation and is usually associated with other intracardiac pathology. Interruption may occur at any level, although it is most commonly seen between the left subclavian artery and the insertion of the ductus arteriosus (type A), followed in frequency by those between the left subclavian and left carotid arteries (type B), or between the left carotid and brachiocephalic arteries (type C). In newborns with an interrupted aortic arch, the ductus arteriosus provides the sole source of blood flow to the descending aorta, and differential oxygen saturations between the right arm (normal saturation) and the legs (decreased saturation) is noted. When the ductus begins to close, severe congestive heart failure, lower extremity hypoperfusion, anuria, and shock usually develop. Patients with an interrupted aortic arch can be supported with prostaglandin E, to keep the ductus patent before surgical repair. As one of the conotruncal malformations, an interrupted aortic arch, especially type B, can be associated with DiGeorge syndrome (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization demonstrates deletion of a segment of chromosome 22q11, known as the DiGeorge critical region.

427.9 Congenital Mitral Stenosis
Daniel Bernstein

Congenital mitral stenosis is a rare anomaly that can be isolated or associated with other defects, the most common being subvalvar and valvar aortic stenosis and coarctation of the aorta (Shone complex). The mitral valve may be funnel-shaped, with thickened leaflets and chordae tendineae that are shortened and deformed. Other mitral valve anomalies associated with stenosis include parachute mitral valve, caused by a single papillary muscle, and double-orifice mitral valve.

If the stenosis is moderate to severe, symptoms usually appear within the 1st yr or 2 of life. These infants have failure to thrive and various degrees of dyspnea and pallor. In some patients, wheezing may be a dominant symptom, and a misdiagnosis of bronchiolitis or reactive airway disease may have been made. Heart enlargement as a result of dilation and hypertrophy of the right ventricle and left atrium is common. Most patients have rumbling apical diastolic murmurs, but the auscultatory findings may be relatively obscure. The 2nd heart sound is loud and split. An opening snap of the mitral valve may be present. The electrocardiogram reveals right ventricular hypertrophy and may show bifid or spiked P waves indicative of left atrial enlargement. Roentgenograms usually show left atrial and right ventricular enlargement and pulmonary congestion in a perihilar or venous pattern. The echocardiogram is characteristic and shows thickened mitral valve leaflets a significant reduction of the mitral valve orifice, abnormal papillary muscle structure (or a single papillary muscle), and an enlarged left atrium with a normal or small left ventricle. A double orifice may also be visualized. Doppler studies demonstrate a mean pressure gradient across the mitral orifice. Associated anomalies such as aortic stenosis and coarctation can be evaluated. Cardiac catheterization is usually performed to confirm the transmitral pressure gradient before surgery. An increase in right ventricular, pulmonary arterial, and pulmonary capillary wedge pressure can be noted. Angiocardiography shows delayed emptying of the left atrium and the small mitral orifice.

The results of surgical treatment depend on the anatomy of the valve, but if the mitral orifice is significantly hypoplastic, reduction of the gradient may be difficult. In some patients, a mitral valve prosthesis is required, and if the valve orifice is too small, the prosthesis may be placed in the supramitral position. However, whatever prosthesis is used, it must be replaced serially as the child grows. These patients must be managed by anticoagulation with warfarin, and complications of excessive and insufficient anticoagulation are fairly common in infancy. Transcatheter balloon valvuloplasty has been used as a palliative procedure with disappointing results, except in the situation of rheumatic mitral stenosis.

Bibliography is available at Expert Consult.

427.10 Pulmonary Venous Hypertension
Daniel Bernstein

A variety of lesions may give rise to chronic pulmonary venous hypertension, which when extreme may result in pulmonary arterial hypertension and right-sided heart failure. These lesions include congenital mitral stenosis, mitral insufficiency, total anomalous pulmonary venous return with obstruction, left atrial myxomas, cor triatriatum (stenosis of a common pulmonary vein), individual pulmonary vein stenosis, and supravalvular mitral rings. Early symptoms can be confused with chronic pulmonary disease such as asthma because of a lack of specific cardiac findings on physical examination. Subtle signs of pulmonary hypertension may be present. The electrocardiogram shows right ventricular hypertrophy with spiked P waves. Roentgenographic studies reveal cardiac enlargement and prominence of the pulmonary veins in the hilar region, the right ventricle and atrium, and the main pulmonary artery; the left atrium is normal in size or only slightly enlarged.

The echocardiogram may demonstrate left atrial myxoma, cor triatriatum, stenosis of one or more pulmonary veins, or a mitral valve abnormality, especially supravalvar mitral ring. Cardiac catheterization excludes the presence of a shunt and demonstrates pulmonary hypertension with elevated pulmonary arterial wedge pressure. Left atrial pressure is normal if the lesion is at the level of the pulmonary veins, but it is elevated if the lesion is at the level of the mitral valve. Selective pulmonary arteriography usually delineates the anatomic lesion. Cor triatriatum, left atrial myxoma, and supravalvular mitral rings can all be successfully managed surgically.

The differential diagnosis includes pulmonary venoocclusive disease, an idiopathic process that produces obstructive lesions in 1 or more pulmonary veins. The cause is uncertain and disease that begins in 1 vein can spread to others. Although it is usually encountered in patients after repair of obstructed total anomalous pulmonary venous return (see Chapter 431.7), it can occur in the absence of congenital heart disease. The patient initially presents with left-sided heart failure on the basis of congested lungs with apparent pulmonary edema. Dyspnea, fatigue, and pleural effusions are common. Left atrial pressure is normal, but pulmonary arterial wedge pressure is usually elevated. A normal wedge pressure may be encountered if collaterals have formed or the wedge recording is performed in an uninvolved segment. Angiographically, the pulmonary veins return normally to the left atrium, but 1 or more pulmonary veins are narrowed, either focally or diffusely.
Bibliography


Studies using lung biopsy have demonstrated pulmonary venous and, occasionally, arterial involvement. Pulmonary veins and venules demonstrate fibrous narrowing or occlusion, and pulmonary artery thrombi may be present. Attempts at surgical repair, balloon dilation, and transcatheter stenting have not significantly improved the generally poor prognosis of these patients. Clinical trials of antiproliferative chemotherapy are currently in progress. Combined heart-lung transplantation (see Chapter 443.2) is often the only alternative therapeutic option.
Pulmonary valvular insufficiency most often accompanies other cardiovascular diseases or may be secondary to severe pulmonary hypertension. Incompetence of the valve is an expected result after surgery for right ventricular outflow tract obstruction, for example, pulmonary valvotomy in patients with valvular pulmonary stenosis or valvotomy with infundibular resection in patients with tetralogy of Fallot. Isolated congenital insufficiency of the pulmonary valve is rare. These patients are usually asymptomatic because the insufficiency is generally mild.

The prominent physical sign is a decrescendo diastolic murmur at the upper and midleft sternal border, which has a lower pitch than the murmur of aortic insufficiency because of the lower pressure involved. Radiographs of the chest show prominence of the main pulmonary arteries, which are dilated. The electrocardiogram is normal or shows minimal right ventricular hypertrophy. Pulsed and color Doppler studies demonstrate retrograde flow from the pulmonary artery to the right ventricle during diastole.

Congenital mitral insufficiency is rare as an isolated lesion and is more often associated with other anomalies. It is most commonly encountered in combination with an atrioventricular septal defect, either an ostium primum defect, or a complete atrioventricular septal defect (see Chapter 426.5). Mitral insufficiency is also seen in patients with dilated cardiomyopathy (see Chapter 439.1) as their left ventricular function deteriorates, secondary to dilation of the valve ring. Mitral insufficiency may also be encountered in conjunction with coarctation of the aorta, ventricular septal defect, corrected transposition of the great vessels, anomalous origin of the left coronary artery from the aorta, or Marfan syndrome. In the absence of other congenital heart disease, endocarditis or rheumatic fever should be suspected in a patient with isolated severe mitral insufficiency (Table 428-1).

In isolated mitral insufficiency, the mitral valve annulus is usually dilated, the chordae tendineae are short and may insert anomalously, and the valve leaflets are deformed. When mitral insufficiency is severe enough to cause clinical symptoms, the left atrium enlarges as a result of the regurgitant flow, and the left ventricle becomes hypertrophied and dilated. Pulmonary venous pressure is increased, and the increased pressure ultimately results in pulmonary hypertension and right ventricular hypertrophy and dilation. Mild lesions produce no symptoms;
Bibliography


the only abnormal sign is the apical holosystolic murmur of mitral regurgitation. Severe regurgitation results in symptoms that can appear at any age, including poor physical development, frequent respiratory infections, fatigue on exertion, and episodes of pulmonary edema or congestive heart failure. Often, a diagnosis of reactive airway disease will have been made because of the similarity in pulmonary symptoms, including wheezing, which may be a dominant finding in infants and young children.

The typical murmur of mitral insufficiency is a high-pitched, apical holosystolic murmur. If the insufficiency is moderate to severe, it is usually associated with a low-pitched, apical mid-diastolic rumbling murmur indicative of increased diastolic flow across the mitral valve. The pulmonary component of the 2nd heart sound will be accentuated in the presence of pulmonary hypertension. The electrocardiogram usually shows bifid P waves consistent with left atrial enlargement, signs of left ventricular hypertrophy, and sometimes signs of right ventricular hypertrophy. Radiographic examination shows enlargement of the left atrium, which at times is massive. The left ventricle is prominent, and pulmonary vascularity is normal or prominent. The echocardiogram demonstrates the enlarged left atrium and ventricle. Color Doppler demonstrates the extent of the insufficiency, and pulsed Doppler of the pulmonary veins detects retrograde flow when mitral insufficiency is severe. Cardiac catheterization shows elevated left atrial pressure. Pulmonary artery hypertension of varying severity may be present. Selective left ventriculography reveals the severity of mitral regurgitation.

Mitral valvuloplasty can result in striking improvement in symptoms and heart size, but in some patients, installation of a prosthetic mechanical mitral valve may be necessary. Before surgery, associated anomalies must be identified.

**428.3 Mitral Valve Prolapse**

Daniel Bernstein

Mitral valve prolapse results from an abnormal mitral valve mechanism that causes billowing of one or both mitral leaflets, especially the posterior cusp, into the left atrium toward the end of systole. The abnormality is predominantly congenital but may not be recognized until adolescence or adulthood. Mitral valve prolapse is usually sporadic, is more common in girls, and may be inherited as an autosomal dominant trait with variable expression. It is common in patients with Marfan syndrome, straight back syndrome, pectus excavatum, scoliosis, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. The dominant abnormal signs are auscultatory, including wheezing, which may be a dominant finding in infants and young children.

The typical murmur of mitral insufficiency is a high-pitched, apical holosystolic murmur. If the insufficiency is moderate to severe, it is usually associated with a low-pitched, apical mid-diastolic rumbling murmur indicative of increased diastolic flow across the mitral valve. The pulmonary component of the 2nd heart sound will be accentuated in the presence of pulmonary hypertension. The electrocardiogram usually shows bifid P waves consistent with left atrial enlargement, signs of left ventricular hypertrophy, and sometimes signs of right ventricular hypertrophy. Radiographic examination shows enlargement of the left atrium, which at times is massive. The left ventricle is prominent, and pulmonary vascularity is normal or prominent. The echocardiogram demonstrates the enlarged left atrium and ventricle. Color Doppler demonstrates the extent of the insufficiency, and pulsed Doppler of the pulmonary veins detects retrograde flow when mitral insufficiency is severe. Cardiac catheterization shows elevated left atrial pressure. Pulmonary artery hypertension of varying severity may be present. Selective left ventriculography reveals the severity of mitral regurgitation.

Mitral valvuloplasty can result in striking improvement in symptoms and heart size, but in some patients, installation of a prosthetic mechanical mitral valve may be necessary. Before surgery, associated anomalies must be identified.

**428.4 Tricuspid Regurgitation**

Daniel Bernstein

Isolated tricuspid regurgitation is generally associated with Ebstein anomaly of the tricuspid valve. Ebstein anomaly may occur either without cyanosis or with varying degrees of cyanosis, depending on the severity of the tricuspid regurgitation and the presence of an atrial-level communication (patent foramen ovale or atrial septal defect). Older children tend to have the acyanotic form, whereas if detected in the newborn period, Ebstein anomaly is usually associated with severe cyanosis (see Chapter 430.7).

Tricuspid regurgitation often accompanies right ventricular dysfunction. When the right ventricle becomes dilated because of volume overload or intrinsic myocardial disease, or both, the tricuspid annulus also enlarges, with resultant valve insufficiency. This form of regurgitation may improve if the cause of the right ventricular dilation is corrected, or it may require surgical plication of the valve annulus. Tricuspid regurgitation is also encountered in newborns with perinatal asphyxia. The cause may be related to an increased susceptibility of the papillary muscles to ischemic damage and subsequent transient papillary muscle dysfunction. Finally, tricuspid regurgitation is seen in up to 30% of children after heart transplantation, which can be a risk factor for graft dysfunction but is also seen as a consequence of valve injury as a result of endomyocardial biopsy.

Bibliography is available at Expert Consult.
Bibliography
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Cyanotic Congenital Heart Disease: Evaluation of the Critically Ill Neonate with Cyanosis and Respiratory Distress

Daniel Bernstein

See also Chapter 101.

A severely ill neonate with cardiorespiratory distress and cyanosis is a diagnostic challenge. The clinician must perform a rapid evaluation to determine whether congenital heart disease is a cause so that potentially lifesaving measures can be instituted. The differential diagnosis of neonatal cyanosis is presented in Table 101-1 in Chapter 101.

CARDIAC DISEASE LEADING TO CYANOSIS

Congenital heart disease produces cyanosis when obstruction to right ventricular outflow causes intracardiac right-to-left shunting or when complex anatomic defects, many unassociated with pulmonary stenosis, cause an admixture of pulmonary and systemic venous return in the heart. Cyanosis from pulmonary edema may also develop in patients with heart failure caused by left-to-right shunts, although the degree is usually less severe. Cyanosis may be caused by persistence of fetal pathways, for example, right-to-left shunting across the foramen ovale and ductus arteriosus in the presence of pulmonary outflow tract obstruction or persistent pulmonary hypertension of the newborn (PPHN) (see Chapter 101.7).

DIFFERENTIAL DIAGNOSIS

The hyperoxia test is 1 method of distinguishing cyanotic congenital heart disease from pulmonary disease. Neonates with cyanotic congenital heart disease are usually not able to significantly raise their arterial PaO\textsubscript{2} during administration of 100% oxygen. If the PaO\textsubscript{2} rises above 150 mm Hg during 100% oxygen administration, an intracardiac right-to-left shunt can usually be excluded, although this is not 100% confirmative, as some patients with cyanotic congenital heart lesions may be able to increase their PaO\textsubscript{2} to >150 mm Hg because of favorable intracardiac streaming patterns. In patients with pulmonary disease, PaO\textsubscript{2} generally increases significantly with 100% oxygen as ventilation-perfusion inequalities are overcome. In infants with cyanosis from a central nervous system disorder, the PaO\textsubscript{2} usually normalizes completely during artificial ventilation. Hypoxia in many heart lesions is profound and constant, whereas in respiratory disorders and in PPHN, arterial oxygen tension often varies with time or changes in ventilator management. Hyperventilation may improve the hypoxia in neonates with PPHN and only occasionally in those with cyanotic congenital heart disease.

Although a significant heart murmur usually suggests a cardiac basis for the cyanosis, several of the more severe cardiac defects (transposition of the great vessels) may not initially be associated with a murmur.

The chest roentgenogram may be helpful in the differentiation of pulmonary and cardiac disease; in the latter, it indicates whether pulmonary blood flow is increased, normal, or decreased.

Two-dimensional echocardiography is the definitive noninvasive test to determine the presence of congenital heart disease. Cardiac catheterization is less often used for diagnostic purposes, and is usually performed to examine structures that are sometime less well visualized by echocardiography, such as distal branch pulmonary arteries or aortopulmonary collateral arteries in patients with tetralogy of Fallot with pulmonary atresia (see Chapter 430.2), coronary arteries and right ventricular sinusoids in patients with pulmonary atresia and intact ventricular septum (see Chapter 430.3). If echocardiography is not immediately available, the clinician caring for a newborn with possible cyanotic heart disease should not hesitate to start a prostaglandin infusion (for a possible ductal-dependent lesion). Because of the risk of hypoventilation associated with prostaglandins, a practitioner skilled in neonatal endotracheal intubation must be available.
Cyanotic Congenital Heart Lesions: Lesions Associated with Decreased Pulmonary Blood Flow

430.1 Tetralogy of Fallot
Daniel Bernstein

Tetralogy of Fallot is one of the conotruncal family of heart lesions in which the primary defect is an anterior deviation of the infundibular septum (the muscular septum that separates the aortic and pulmonary outflows). The consequences of this deviation are the 4 components: (1) obstruction to right ventricular outflow (pulmonary stenosis), (2) a malalignment type of ventricular septal defect (VSD), (3) dextroposition of the aorta so that it overrides the ventricular septum, and (4) right ventricular hypertrophy (Fig. 430-1). Obstruction to pulmonary arterial blood flow is usually at both the right ventricular infundibulum (subpulmonic area) and the pulmonary valve. The main pulmonary artery may be small, and various degrees of branch pulmonary artery stenosis may be present. Complete obstruction of right ventricular outflow (tetralogy with pulmonary atresia) is classified as an extreme form of tetralogy of Fallot (see Chapter 430.2). The degree of pulmonary outflow obstruction determines the degree of the patient's cyanosis and the age of first presentation.

PATHOPHYSIOLOGY
The pulmonary valve annulus may range from being nearly normal in size to being severely hypoplastic. The valve itself is often bicuspid or unicuspid and, occasionally, is the only site of stenosis. More commonly, the subpulmonic or infundibular muscle, known as the crista supraventricularis, is hypertrophic, which contributes to the subvalvar stenosis and results in an infundibular chamber of variable size and contour. When the right ventricular outflow tract is completely
obstructed (pulmonary atresia), the anatomy of the branch pulmonary arteries is extremely variable. A main pulmonary artery segment may be in continuity with right ventricular outflow, separated by a fibrous but imperforate pulmonary valve; the main pulmonary artery may be moderately or severely hypoplastic but still supply part or all of the pulmonary bed; or the entire main pulmonary artery segment may be absent. Occasionally, the branch pulmonary arteries may be discontinuous. Pulmonary blood flow may be supplied by a patent ductus arteriosus (PDA) or by multiple aortopulmonary collateral arteries (MAPCAs) arising from the ascending and/or descending aorta and supplying various lung segments.

The VSD is usually nonrestrictive and large, is located just below the aortic valve, and is related to the posterior and right aortic cusps. Rarely, the VSD may be in the inlet portion of the ventricular septum (atrioventricular septal defect). The normal fibrous continuity of the mitral and aortic valves is usually maintained, and if not (because of the presence of a subaortic muscular conus) the classification is usually that of double-outlet right ventricle (see Chapter 430.5). The aortic arch is right sided in 20% of cases, and the aortic root is usually large and overrides the VSD to varying degrees. When the aorta overrides the VSD by more than 50% and if there is a subaortic conus, this defect is classified as a form of double-outlet right ventricle; however, the circulatory dynamics are the same as that of tetralogy of Fallot.

Systemic venous return to the right atrium and right ventricle is normal. When the right ventricle contracts in the presence of marked pulmonary stenosis, blood is shunted across the VSD into the aorta. Persistent arterial desaturation and cyanosis result, the degree dependent on the severity of the pulmonary obstruction. Pulmonary blood flow, when severely restricted by the obstruction to right ventricular outflow, may be supplemented by a PDA. Peak systolic and diastolic pressures in each ventricle are similar and at systemic level. A large pressure gradient occurs across the obstructed right ventricular outflow tract, and pulmonary arterial pressure is either normal or lower than normal. The degree of right ventricular outflow obstruction determines the timing of the onset of symptoms, the severity of cyanosis, and the degree of right ventricular hypertrophy. When obstruction to right ventricular outflow is mild to moderate and a balanced shunt is present across the VSD, the patient may not be visibly cyanotic (acyanotic or “pink” tetralogy of Fallot). When obstruction is severe, cyanosis will be present from birth and worsen when the ductus arteriosus begins to close.

**CLINICAL MANIFESTATIONS**

Infants with mild degrees of right ventricular outflow obstruction may initially be seen with heart failure caused by a ventricular-level left-to-right shunt. Often, cyanosis is not present at birth; but with increasing hypertrophy of the right ventricular infundibulum as the patient grows, cyanosis occurs later in the 1st yr of life. In infants with severe degrees of right ventricular outflow obstruction, neonatal cyanosis is noted immediately. In these infants, pulmonary blood flow may be partially or nearly totally dependent on flow through the ductus arteriosus. When the ductus begins to close in the 1st few hr or days of life, severe cyanosis and circulatory collapse may occur. Older children with long-standing cyanosis who have not undergone surgery may have dusky blue skin, gray sclerae with engorged blood vessels, and marked clubbing of the fingers and toes. Chapter 434 describes the extracardiac manifestations of long-standing cyanotic congenital heart disease.

In older children with unrepaired tetralogy, dyspnea occurs on exertion. They may play actively for a short time and then sit or lie down. Older children may be able to walk a block or so before stopping to rest. Characteristically, children assume a squatting position for the relief of dyspnea caused by physical effort; the child is usually able to resume physical activity after a few minutes of squatting. These findings occur most often in patients with significant cyanosis at rest.

Paroxysmal hypercyanotic attacks (hypoxic, “blue,” or “tet” spells) are a particular problem during the 1st 2 yr of life. The infant becomes hyperpneic and restless, cyanosis increases, gasping respirations ensue, and syncope may follow. The spells occur most frequently in the morning on initially awakening or after episodes of vigorous crying. Temporary disappearance or a decrease in intensity of the systolic murmur is usual as flow across the right ventricular outflow tract diminishes. The spells may last from a few minutes to a few hours. Short episodes are followed by generalized weakness and sleep. Severe spells may progress to unconsciousness and, occasionally, to convulsions or hemiparesis. The onset is usually spontaneous and unpredictable. Spells are associated with reduction of an already compromised pulmonary blood flow, which, when prolonged, results in severe systemic hypoxia and metabolic acidosis. Infants who are only mildly cyanotic at rest are often more prone to the development of hypoxic spells because they have not acquired the homeostatic mechanisms to tolerate rapid lowering of arterial oxygen saturation, such as polycythemia.

Depending on the frequency and severity of hypercyanotic attacks, 1 or more of the following procedures should be instituted in sequence: (1) placement of the infant on the abdomen in the knee-chest position while making certain that the infant’s clothing is not constrictive, (2) administration of oxygen (although increasing inspired oxygen will not reverse cyanosis caused by intracardiac shunting), and (3) injection of morphine subcutaneously in a dose not in excess of 0.2 mg/kg. Calming and holding the infant in a knee-chest position may abort progression of an early spell. Premature attempts to obtain blood samples may cause further agitation and be counterproductive.

Because metabolic acidosis develops when arterial PO2 is <40 mm Hg, rapid correction (within several minutes) with intravenous administration of sodium bicarbonate is necessary if the spell is unusually severe and the child shows a lack of response to the foregoing therapy. Recovery from the spell is usually rapid once the pH has returned to normal. Repeated blood pH measurements may be necessary because rapid

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**Figure 430-1 Physiology of the tetralogy of Fallot.** Circled numbers represent oxygen saturation values. The numbers next to the arrows represent volumes of blood flow (in L/min/m²). Atrial (mixed venous) oxygen saturation is decreased because of the systemic hypoxemia. A volume of 3 L/min/m² of desaturated blood enters the right atrium and traverses the tricuspid valve. Two liters flows through the right ventricular outflow tract into the lungs, whereas 1 L shunts right to left through the ventricular septal defect (VSD) into the ascending aorta. Thus, pulmonary blood flow is two-thirds normal (Qp:Qs [pulmonary-to-systemic blood flow ratio] of 0.7:1). Blood returning to the left atrium is fully saturated. Only 2 L of blood flows across the mitral valve. Oxygen saturation in the left ventricle may be slightly decreased because of right-to-left shunting across the VSD. Two liters of saturated left ventricular blood mixing with 1 L of desaturated right ventricular blood is ejected into the ascending aorta. Aortic saturation is decreased, and cardiac output is normal.
Diagnosis

The typical radiologic configuration as seen in the anteroposterior view consists of a narrow base, concavity of the left heart border in the area usually occupied by the pulmonary artery, and normal overall heart size. The hypertrophied right ventricle causes the rounded apical shadow to be uptilted so that it is situated higher above the diaphragm than normal and pointing horizontally to the left chest wall. The cardiac silhouette has been likened to that of a boot (“coeur en sabot”) (Fig. 430-2). The hilar areas and lung fields are relatively clear because of diminished pulmonary blood flow or the small size of the pulmonary arteries, or both. The aorta is usually large, and in approximately 20% of patients it arches to the right, which results in an indentation of the leftward-positioned air-filled tracheobronchial shadow in the anteroposterior view.

The electrocardiogram demonstrates right axis deviation and evidence of right ventricular hypertrophy. A dominant R wave appears in the right precordial chest leads (Rs, R, qR, qRs) or an RSR' pattern. In some cases, the only sign of right ventricular hypertrophy may initially be a positive T wave in leads V1R and V2. The P wave is tall and peaked suggesting right atrial enlargement (see Fig. 423-6 in Chapter 423).

Two-dimensional echocardiography establishes the diagnosis (Fig. 430-3) and provides information about the extent of aortic override of the septum, the location and degree of the right ventricular outflow tract obstruction, the size of the pulmonary valve annulus and main and proximal branch pulmonary arteries, and the side of the aortic arch. The echocardiogram is also useful in determining whether or not a PDA is supplying a portion of the pulmonary blood flow. In a patient without pulmonary atresia, echocardiography usually obviates the need for catheterization before surgical repair. However, in patients with pulmonary atresia, catheterization is necessary to image the source of blood supply to and size of each lung segment.

Cardiac catheterization demonstrates a systolic pressure in the right ventricle equal to the systemic pressure, since the right ventricle is connected directly to the overriding aorta. If the pulmonary artery is entered, the pressure is markedly decreased, although crossing the right ventricular outflow tract, especially in severe cases, may precipitate a tet spell. Pulmonary arterial pressure is usually lower than normal, in the range of 5-10 mm Hg. The level of arterial oxygen saturation depends on the magnitude of the right-to-left shunt; in “pink tets,” the systemic oxygen saturation may be normal, whereas in a moderately cyanotic patient at rest, it is usually 75-85%.

Selective right ventriculography will demonstrate all of the anatomic features. Contrast medium outlines the heavily trabeculated right ventricle. The infundibular stenosis varies in length, width, contour, and distensibility (Fig. 430-4). The pulmonary valve is usually thickened, and the annulus may be small. In patients with pulmonary atresia and VSD, echocardiography alone is not adequate to assess the anatomy of the pulmonary arteries and MAPCAs. Cardiac CT is extremely helpful, and cardiac catheterization with injection into each arterial collateral is indicated. Complete and accurate information regarding the size and peripheral distribution of the main pulmonary arteries and any collateral vessels (MAPCAs) is important when evaluating these children as surgical candidates.

Aortography or coronary arteriography outlines the course of the coronary arteries. In 5-10% of patients with the tetralogy of Fallot, coronary artery abnormalities may be present, most commonly an aberrant coronary artery crossing over the right ventricular outflow.
surgery, any residual pulmonic stenosis or VSD. Heart failure is not a usual feature in patients with tetralogy of Fallot, with the exception of some young infants with “pink” or acyanotic tetralogy of Fallot. As the degree of pulmonary obstruction worsens with age, the symptoms of heart failure resolve and eventually the patient experiences cyanosis often by 6-12 mo of age. These patients are at increased risk for hypercyanotic spells at this time.

ASSOCIATED ANOMALIES

A PDA may be present, and defects in the atrial septum are occasionally seen. A right aortic arch occurs in ~20% of patients, and other anomalies of the pulmonary arteries and aortic arch may also be seen. Persistence of a left superior vena cava draining into the coronary sinus is common but not a concern. Multiple VSDs are occasionally present and must be diagnosed before corrective surgery. Coronary artery anomalies are present in 5-10% and can complicate surgical repair. Tetralogy of Fallot may also occur with an atrioventricular septal defect, often associated with Down syndrome.

Congenital absence of the pulmonary valve produces a distinct syndrome that is usually marked by signs of upper airway obstruction (see Chapter 428.1). Cyanosis may be absent, mild, or moderate; the heart is large and hyperdynamic; and a loud-to-and-fro murmur is present. Marked aneurysmal dilation of the main and branch pulmonary arteries results in compression of the bronchi and then produces stridulous or wheezing respirations and recurrent pneumonia. If the airway obstruction is severe, reconstruction of the trachea at the time of corrective cardiac surgery may be required to alleviate the symptoms.

Absence of a branch pulmonary artery, most often the left, should be suspected if the roentgenographic appearance of the pulmonary vasculature differs on the 2 sides; absence of a pulmonary artery is often associated with hypoplasia of the affected lung. It is important to recognize the absence of a pulmonary artery because occlusion of the remaining pulmonary artery during surgery seriously compromises the already reduced pulmonary blood flow.

As 1 of the conotruncal malformations, tetralogy of Fallot can be associated with DiGeorge syndrome or Shprintzen velocardiofacial syndrome, also known by the acronym CATCH 22 (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cyto genetic analysis using fluorescence in situ hybridization demonstrates deletions of a large segment of chromosome 22q11.2 known as the DiGeorge critical region. Deletion or mutation of the gene encoding the transcription factor Tbx1 has been implicated as a possible cause of DiGeorge syndrome, although several other genes have been identified as possible candidates or modifier genes.

TREATMENT

Treatment of tetralogy of Fallot depends on the severity of the right ventricular outflow tract obstruction. Infants with severe tetralogy require urgent medical treatment and surgical intervention in the neonatal period. Therapy is aimed at providing an immediate increase in pulmonary blood flow to prevent the sequelae of severe hypoxia. The infant should be transported to a medical center adequately equipped to evaluate and treat neonates with congenital heart disease under optimal conditions. Prolonged, severe hypoxia may lead to shock, respiratory failure, and intractable acidosis and will significantly reduce the chance of survival, even when surgically amenable lesions are present. It is critical that normal body temperature be maintained during the transfer because cold increases oxygen consumption, which places additional stress on a cyanotic infant, whose oxygen delivery is already limited. Blood glucose levels should be monitored because hypoglycemia is more likely to develop in infants with cyanotic heart disease.

Neonates with marked right ventricular outflow tract obstruction may deteriorate rapidly because, as the ductus arteriosus begins to close, pulmonary blood flow is further compromised. The intravenous administration of prostaglandin E₃ (0.01-0.20 µg/kg/min), a potent and specific relaxant of ductal smooth muscle, causes dilation of the ductus arteriosus and usually provides adequate pulmonary blood flow.
until a surgical procedure can be performed. This agent should be administered intravenously as soon as cyanotic congenital heart disease is clinically suspected and continued through the preoperative period and during cardiac catheterization. Because prostaglandin can cause apnea, an individual skilled in neonatal intubation should be readily available.

Infants with less-severe right ventricular outflow tract obstruction who are stable and awaiting surgical intervention require careful observation. Acyanotic patients can fairly quickly progress to having cyanotic episodes. Prevention or prompt treatment of dehydration is important to avoid hemococoncentration and possible thrombotic episodes. Oral propranolol (0.5-1 mg/kg every 6 hr) had been used in the past to decrease the frequency and severity of hypercyanotic spells, but with the excellent surgical results available today, surgical treatment is now indicated as soon as spells begin.

Infants with symptoms and severe cyanosis in the 1st mo of life usually have marked obstruction of the right ventricular outflow tract. Two options are available in these infants. The first is corrective open heart surgery performed in early infancy and even in the newborn period in critically ill infants. This approach has widespread acceptance today with excellent short- and long-term results and has supplanted palliative shunts (see later) for most cases. Early total repair carries the theoretical advantage that early physiologic correction allows for improved growth of the branch pulmonary arteries. In infants with less-severe cyanosis who can be maintained with good growth and absence of hypercyanotic spells, primary repair is performed electively at between 4 and 6 mo of age.

Corrective surgical therapy consists of relief of the right ventricular outflow tract obstruction by resecting obstructive muscle bundles and by patch closure of the VSD. If the pulmonary valve is stenotic, as it usually is, a valvotomy is performed. If the pulmonary valve annulus is too small or the valve is extremely thickened, a valvectomy may be performed, the pulmonary valve annulus split open, and a transanular patch placed across the pulmonary valve ring. The surgical risk of total correction in major centers is <5%. A right ventriculotomy was once the standard approach; a transatrial–transpulmonary approach is routinely performed to reduce the long-term risks of a large right ventriculotomy. In patients in whom repair has been delayed to childhood, increased bleeding in the immediate postoperative period may be a complicating factor because of their extreme polycythemia.

The second option, more common in previous years, is a palliative systemic-to-pulmonary artery shunt (Blalock-Taussig shunt) performed to augment pulmonary artery blood flow. The rationale for this surgery, previously the only option for these patients, is to augment pulmonary blood flow to decrease the amount of hypoxia and improve linear growth, as well as augment growth of the branch pulmonary arteries. The modified Blalock-Taussig shunt is currently the most common aortopulmonary shunt procedure and consists of a Gore-Tex conduit anastomosed side to side from the subclavian artery to the homolateral branch of the pulmonary artery (Fig. 430-5). Sometimes the shunt is brought directly from the ascending aorta to the main pulmonary artery; in this case, it is called a central shunt. Postoperative complications after a Blalock-Taussig shunt include chylothorax, diaphragmatic paralysis, and Horner syndrome. Postoperative pulmonary overcirculation leading to symptoms of cardiac failure may be caused by too large a shunt; Chapter 442 describes its treatment. Vascular problems other than a diminished radial pulse and occasional long-term arm length discrepancy are rarely seen in the upper extremity supplied by the subclavian artery used for the anastomosis.

After a successful shunt procedure, cyanosis diminishes. The development of a continuous murmur over the lung fields after the operation indicates a functioning anastomosis. A good continuous shunt murmur may not be heard until several days after surgery. The duration of symptomatic relief is variable. As the child grows, more pulmonary blood flow is needed and the shunt eventually becomes inadequate. When increasing cyanosis develops rapidly, thrombosis of the shunt should be suspected, often requiring emergent surgery.

Currently, Blalock-Taussig shunts are usually reserved for patients with comorbidities, such as other major congenital anomalies or prematurity, that would make full repair a higher risk option. However, many surgeons still recommend full repair in these situations, being preferable to the combined risks of a staged procedure, and successful repairs have been done even in small premature infants.

PROGNOSIS

After successful total correction, patients are generally asymptomatic and are able to lead unrestricted lives. Uncommon immediate postoperative problems include right ventricular failure, transient heart block, residual VSD with left-to-right shunting, and myocardial infarction from interruption of an aberrant coronary artery. Postoperative heart failure (particularly in patients with a large transannular outflow patch) may require anticongestive therapy. The long-term effects of isolev LDL, surgically induced pulmonary valvular insufficiency are still being defined as more patients with repaired tetralogy of Fallot reach middle age, but insufficiency is generally well-tolerated through adolescence. Many patients after tetralogy repair and all of those with transannular patch repairs have a to-and-fro murmur at the left sternal border, usually indicative of mild outflow obstruction and mild to moderate pulmonary insufficiency. Patients with more marked pulmonary valve insufficiency may also have moderate to more severe degrees of right ventricular enlargement and may develop tricuspid regurgitation as the tricuspid valve annulus dilates. These patients will develop a holosystolic murmur at the lower left sternal border. Patients with a severe residual gradient across the right ventricular outflow tract may require reoperation, but mild to moderate degrees of residual obstruction usually do not require reintervention.

Follow-up of patients 5-20 yr after surgery indicates that the marked improvement in symptoms is generally maintained. Asymptomatic patients nonetheless have lower than normal exercise capacity, maximal heart rate, and cardiac output. These abnormal findings are more common in patients who underwent placement of a transannular outflow tract patch and may be less frequent when surgery is performed at an early age. As these children move into adolescence and adulthood, some (more commonly those with transannular patches) will develop right ventricular dilation as a result of severe pulmonary
regurgitation. After reaching adulthood, careful lifelong follow-up by a specialist in adult congenital heart disease is important. Serial echocardiography and the more quantitative magnetic resonance angiography are valuable tools for assessing the degree of right ventricular dilation, the presence of right ventricular dysfunction, and for quantifying the regurgitant fraction. Valve replacement is indicated for those patients with increasing right ventricular dilation and tricuspid regurgitation. For patients requiring valve replacement, new nonsurgical options are being developed. Stent valves, which can be delivered in the cardiac catheterization lab, have been used successfully in many patients with repaired tetralogy of Fallot. These are being used predominantly in patients who have previously had a homograft or other artificial conduit placed between the right ventricular and pulmonary arteries.

Conduction disturbances can occur after surgery. The atrioventricular node and the bundle of His and its divisions are in close proximity to the VSD and may be injured during surgery; however, permanent complete heart block after tetralogy repair is rare. When present, it should be treated by placement of a permanently implanted pacemaker. Even transient complete heart block in the immediate postoperative period is rare; it may be associated with an increased incidence of late-onset complete heart block and sudden death. In contrast, right bundle-branch block is quite common on the postoperative electrocardiogram. The duration of the QRS interval has been shown to predict both the presence of residual hemodynamic derangement and the long-term risk of arrhythmia and sudden death. Research is ongoing to determine the effectiveness of biventricular pacing (in which a pacemaker is used to resynchronize the activation of the right and left ventricles) in improving hemodynamics in those patients with long ventricular conduction delays.

A number of children have premature ventricular beats after repair of the tetralogy of Fallot. These beats are of concern in patients with residual hemodynamic abnormalities; 24 hr electrocardiographic (Holter) monitoring studies should be performed to be certain that occult short episodes of ventricular tachycardia are not occurring. Exercise studies may be useful in provoking cardiac arrhythmias that are not apparent at rest. In the presence of complex ventricular arrhythmias or severe residual hemodynamic abnormalities, prophylactic antiarrhythmic therapy, catheter ablation, or implantation of an implantable defibrillator is warranted. Rerepair is indicated if significant residual right ventricular outflow obstruction or severe pulmonary insufficiency is present because arrhythmias may improve after hemodynamics is restored to a more normal level.

Bibliography is available at Expert Consult.

430.2 Tetralogy of Fallot with Pulmonary Atresia
Daniel Bernstein

PATHOPHYSIOLOGY
Tetralogy of a Fallot with pulmonary atresia is the most extreme form of the tetralogy of Fallot. The pulmonary valve is atretic (absent), and the pulmonary trunk may be hypoplastic or atretic as well. The entire right ventricular output is ejected into the aorta. Pulmonary blood flow is then dependent on collateral vessels or MAPCAs, or, rarely, on a PDA. The ultimate prognosis depends on the degree of development of the branch pulmonary arteries, which needs to be assessed by cardiac catheterization. If the pulmonary arteries are severely hypoplastic and fail to grow after palliative shunt procedures, heart-lung transplantation may be the only therapy (see Chapter 443.2). Pulmonary atresia with VSD is also associated with the 22q11.2 deletion and DiGeorge syndrome. The association of severe tracheomalacia or bronchomalacia with these severe forms of tetralogy/pulmonary atresia may complicate postoperative recovery.

CLINICAL MANIFESTATIONS
Patients with pulmonary atresia and VSD have findings similar to those in patients with severe tetralogy of Fallot. Cyanosis usually appears within the 1st few hr or days after birth; however, the prominent systolic murmur associated with the tetralogy is usually absent. The 1st heart sound may be followed by an ejection click caused by the enlarged aortic root, the 2nd heart sound is single and loud, and continuous murmurs of collateral flow may be heard over the entire precordium, both anteriorly and posteriorly. Most patients are moderately cyanotic and are initially stabilized with a prostaglandin E₂, infusion pending cardiac catheterization or CT scan to further delineate the anatomy. Patients with several large MAPCAs may be less cyanotic and, once the diagnosis is confirmed, can be taken off prostaglandin while awaiting palliative surgical intervention. Some patients may even develop symptoms of heart failure caused by increased pulmonary blood flow via these collateral vessels.

DIAGNOSIS
The chest roentgenogram demonstrates a varying heart size, depending on the amount of pulmonary blood flow, a concavity at the position of the pulmonary arterial segment, and often the reticular pattern of bronchial collateral flow. The electrocardiogram shows right ventricular hypertrophy. The echocardiogram identifies aortic override, a thick right ventricular wall, and atresia of the pulmonary valve. Pulsed and color Doppler echocardiographic studies show an absence of forward flow through the pulmonary valve, with pulmonary blood flow being supplied by MAPCAs, which can usually be seen arising from the descending aorta. At cardiac catheterization, right ventriculography reveals a large aorta, opacified immediately by passage of contrast medium through the VSD, but with no dye entering the lungs through the right ventricular outflow tract. Careful delineation of the native pulmonary arteries, if present, to determine whether they are continuous or discontinuous and whether they arborize to all lung segments is important in planning surgical repair. The location and arborization of all MAPCAs and the presence of any localized stenosis are determined by selective contrast injection. CT angiography has recently been utilized to assist in mapping the extent of MAPCA arborization.

TREATMENT
The surgical procedure of choice depends on whether the main pulmonary artery segment is present and, if so, on the size and branching pattern of the branch pulmonary arteries. If these arteries are well developed, a one-stage surgical repair with a homograft conduit between the right ventricle and pulmonary arteries and closure of the VSD is feasible. If the pulmonary arteries are hypoplastic, extensive reconstruction may be required. This usually involves several staged surgical procedures. If the native pulmonary artery is present but small, a connection made between the aorta and the hypoplastic native pulmonary artery (aortopulmonary window) in the newborn period induces growth. At 3-4 mo of age, the multiple MAPCAs are gathered together (unifocalization procedure) and eventually incorporated into the final repair along with the native pulmonary arteries. This may be accomplished through successive lateral thoracotomies, or through a single midline sternotomy if the anatomy is more favorable.

To be a candidate for full repair, the pulmonary arteries must be of adequate size to accept the full volume of right ventricular output. Complete repair includes closure of the VSD and placement of a homograft conduit from the right ventricle to the pulmonary artery. At the time of reparative surgery, previous shunts are taken down. Because of patient growth as well as homograft narrowing due to proliferation of intimal tissue and calcification, replacement of the homograft conduit replacement is usually required in later life, and multiple replacements may be needed. Many of these patients are candidates for placement of a transcatheter stent valve in the pulmonary position. Patients with obstruction of the very distal branches of the pulmonary arteries may undergo repeat surgical procedures or transcatheter balloon dilation.
Bibliography
of the multiple branch pulmonary arterial stenosis. Careful follow-up is warranted for these patients to ensure maximal chance of growth of all pulmonary artery segments.

Bibliography is available at Expert Consult.

430.3 Pulmonary Atresia with Intact Ventricular Septum

Daniel Bernstein

PATHOPHYSIOLOGY

In pulmonary atresia with an intact ventricular septum, the pulmonary valve leaflets are completely fused to form a membrane and the right ventricular outflow tract is atretic. Because no VSD is present, no egress of blood from the right ventricle can occur. Any blood that enters the right ventricle will regurgitate back across the tricuspid valve into the right atrium. Right atrial pressure increases, and blood shunts via the foramen ovale into the left atrium, where it mixes with pulmonary venous blood and enters the left ventricle (Fig. 430-6). The combined left and right ventricular output is pumped solely by the left ventricle into the aorta. In a newborn with pulmonary atresia, the only source of pulmonary blood flow occurs via a PDA. The right ventricle and tricuspid valve are usually hypoplastic, although the degree of hypoplasia varies considerably. Patients who have a small right ventricular cavity also tend to be those with the smallest tricuspid valve annulus, which limits right ventricular inflow. Patients with pulmonary atresia and intact ventricular septum may have coronary sinusoidal channels within the right ventricular wall that communicate directly with the coronary arterial circulation. The high right ventricular pressure results in desaturated blood flowing retrograde via these channels into the coronary arteries. Sometimes there are also stenoses of the coronary arteries proximal to where the sinusoids enter, so that distal coronary artery flow is dependent on flow from the right ventricle (known as right ventricle-dependent coronary circulation). The prognosis in patients with these sinusoids and proximal stenosis of the coronary arteries is more guarded than in those patients without sinusoids or with sinusoids but no coronary stenoses. Rarely, the proximal coronary artery may be totally absent.

CLINICAL MANIFESTATIONS

As the ductus arteriosus closes in the 1st hr and days of life, infants with pulmonary atresia and an intact ventricular septum become markedly cyanotic because their only source of pulmonary blood flow is removed. Untreated, most patients die within the 1st wk of life. Physical examination reveals severe cyanosis and respiratory distress. The 2nd heart sound, representing only aortic closure, is single and loud. Often, no murmurs are audible; sometimes a systolic or continuous murmur can be heard secondary to ductal blood flow. A harsh holosystolic murmur may be heard at the lower left sternal border if there is significant tricuspid regurgitation.

DIAGNOSIS

The electrocardiogram shows a frontal QRS axis between 0 and +90 degrees, the amount of leftward shift reflecting the degree of hypoplasia of the right ventricle. Tall, spiked P waves indicate right atrial enlargement. QRS voltages are consistent with left ventricular dominance or hypertrophy; right ventricular forces are decreased in proportion to the decreased size of the right ventricular cavity. Most patients with small right ventricles have decreased right ventricular forces, but, occasionally, patients with larger, thickened right ventricular cavi-
ties may have evidence of right ventricular hypertrophy. The chest roentgenogram shows decreased pulmonary vascularity, the degree depending on the size of the branch pulmonary arteries and the patency of the ductus. Unlike in patients with pulmonary atresia and tetrology of Fallot, the presence of major collateral vessels (MAPCAs) is rare.

The 2-dimensional echocardiogram is useful in estimating right ventricular dimensions and the size of the tricuspid valve annulus, which have been shown to be of prognostic value. Echocardiography can often suggest the presence of sinusoidal channels but cannot be used to evaluate coronary stenoses. Thus, cardiac catheterization is necessary for complete evaluation. Pressure measurements reveal right atrial and right ventricular hypertension. Ventrilography demonstrates the size of the right ventricular cavity, the atretic right ventricular outflow tract, the degree of tricuspid regurgitation, and the presence or absence of intramycocardial sinusoids filling the coronary vessels. Aortography shows filling of the pulmonary arteries via the PDA and is helpful in determining the size and branching patterns of the pul
monary arterial bed. An aortogram, or if necessary selective coronary angiography is performed to evaluate for the presence of proximal coronary artery stenosis (right ventricular dependent coronary circulation).

TREATMENT

Infusion of prostaglandin E (0.01-0.20 µg/kg/min) is usually effective in keeping the ductus arteriosus open before intervention, thus reduc
ing hypoxemia and acidemia before surgery. The choice of surgical procedure depends on whether there is an RV dependent coronary circulation and on the size of the right ventricular cavity. In patients with only mild to moderate right ventricular hypoplasia without sinusoids, or in patients with sinusoids but no evidence of coronary steno
ses, a surgical pulmonary valvotomy is carried out to relieve outflow obstruction. Often, the right ventricular outflow tract is widened with a patch. To preserve adequate pulmonary blood flow, an aortopulmo
nary shunt may also be performed during the same procedure. An alternative approach uses interventional catheterization, in which the imperforate pulmonary valve is first punctured either with a wire or a radiofrequency ablation catheter, followed by a balloon valvuloplasty.
Bibliography


If this course is taken, it may take days to weeks before the right ventricular muscle regresses enough for the patient to be weaned from prostaglandin, and many of these patients will still require surgical intervention. The aim of surgery or interventional catheterization is to encourage growth of the right ventricular chamber by allowing some forward flow through the pulmonary valve while using the shunt to ensure adequate pulmonary blood flow. Later, if the tricuspid valve annulus and right ventricular chamber grow to adequate size, the shunt is taken down and any remaining atrial level shunt can be closed. If the right ventricular chamber remains too small for use as a pulmonary ventricle, then the patient is treated as a single ventricle circulation, with a Glenn procedure followed by a modified Fontan procedure (see Chapter 430.4), allowing blood to bypass the hypoplastic right ventricle by flowing to the pulmonary arteries directly from the venae cavae. When coronary artery stenoses are present and retrograde coronary perfusion occurs from the right ventricle via myocardial sinuoids, the prognosis is more guarded because of a higher risk of arrhythmias, coronary ischemia, and sudden death. It is important for these patients not to try to open the right ventricular outflow tract, as dropping the right ventricular pressure will reduce coronary perfusion, leading to ischemia. These patients are usually treated with an aortopulmonary shunt, followed by the Glenn and Fontan procedure. Although at higher risk than those without coronary stenoses, recent reports show good success with this approach. A small number of these infants, especially those with total atresia of a proximal coronary artery, are referred instead for heart transplantation.

Bibliography is available at Expert Consult.

**430.4 Tricuspid Atresia**

Daniel Bernstein

**PATHOPHYSIOLOGY**

In tricuspid atresia, no outlet from the right atrium to the right ventricle is present; the entire systemic venous return leaves the right atrium and enters the left side of the heart by means of the foramen ovale or, most often, through an atrial septal defect (Fig. 430-7). The physiology of the circulation and the clinical presentation will depend on the presence of other congenital heart defects, most notably on whether the great vessels are normally related or are transposed (aorta arising from the right ventricle, pulmonary artery from the left ventricle). In patients with normally related great vessels, left ventricular blood supplies the systemic circulation via the aorta. Blood also usually flows into the right ventricle via a VSD (if the ventricular septum is intact, the right ventricle will be completely hypoplastic and pulmonary atresia will be present [see Chapter 430.3]). Pulmonary blood flow (and thus the degree of cyanosis) depends on the size of the VSD and the presence and severity of any associated pulmonic stenosis. Pulmonary blood flow may be augmented by or be totally dependent on a PDA. The inflow portion of the right ventricle is always missing in these patients, but the outflow portion is of variable size. The clinical presentation of patients with tricuspid atresia and normally related great vessels will depend on the degree of pulmonary obstruction. Patients with at least moderate degrees of pulmonary stenosis are recognized in the early days or weeks of life by decreased pulmonary blood flow and cyanosis. Alternatively, in those with a large VSD and minimal or no right ventricular outflow obstruction, pulmonary blood flow may be high; these patients have only mild cyanosis and present with signs of pulmonary overcirculation and heart failure.

In patients with tricuspid atresia and transposition of the great arteries, left ventricular blood flows directly into the pulmonary artery, whereas systemic blood must traverse the VSD and right ventricle to reach the aorta. In these patients, pulmonary blood flow is usually massively increased and heart failure develops early. If the VSD is restrictive, aortic blood flow may be compromised. Coarctation of the aorta is not uncommon in this setting.

**CLINICAL MANIFESTATIONS**

Some degree of cyanosis is usually evident at birth, with the extent depending on the degree of limitation to pulmonary blood flow (as noted above). An increased left ventricular impulse may be noted, in contrast to most other causes of cyanotic heart disease, in which an increased right ventricular impulse is usually present. The majority of patients have holosystolic murmurs audible along the left sternal border; the 2nd heart sound is usually single. Pulses in the lower extremities may be weak or absent in the presence of transposition with coarctation of the aorta. Patients with tricuspid atresia are at risk for spontaneous narrowing or even closure of the VSD, which can occasionally occur rapidly and lead to a marked decrease in systemic oxygen saturation.

**DIAGNOSIS**

Radiologic studies show either pulmonary undercirculation (usually in patients with normally related great vessels) or overcirculation (usually in patients with transposed great vessels). Left axis deviation and left ventricular hypertrophy are generally noted on the electrocardiogram (except in those patients with transposition of the great arteries), and these features distinguish tricuspid atresia from most other cyanotic heart lesions. Thus the combination of cyanosis and left axis deviation on the electrocardiogram is highly suggestive of tricuspid atresia. In the right precordial leads, the normally prominent R wave is replaced by an rS complex. The left precordial leads show a qR complex, followed by a normal, flat, biphasic, or inverted T wave. RV, is normal or tall, and SV, is generally deep. The P waves are usually biphasic, with the initial component tall and spiked in lead II. Two-dimensional echocardiography reveals the presence of a fibromuscular membrane in place of a tricuspid valve, a variably small right ventricle, VSD, and the large left ventricle (Fig. 430-8). The relationship of the great vessels (normal or transposed) can be determined. The degree of
Bibliography
obstruction at the level of the VSD or at the right ventricular outflow tract can be determined by Doppler examination. Blood flow through a patent ductus can be evaluated by color flow and pulsed Doppler.

Cardiac catheterization, indicated usually only if questions remain after echocardiography, shows normal or slightly elevated right atrial pressure with a prominent a wave. If the right ventricle is entered through the VSD, the pressure may be lower than on the left if the VSD is restrictive in size. Right atrial angiography shows immediate opacification of the left atrium from the right atrium followed by left ventricular filling and visualization of the aorta. Absence of direct flow to the right ventricle results in an angiographic filling defect between the right atrium and the left ventricle.

**TREATMENT**

Management of patients with tricuspid atresia depends on the adequacy of pulmonary blood flow. Severely cyanotic neonates should be maintained on an intravenous infusion of prostaglandin E1 (0.01-0.20 µg/kg/min) until a surgical aortopulmonary shunt procedure can be performed to increase pulmonary blood flow. The Blalock-Taussig procedure (see Chapter 430.1) or a variation is the preferred anastomosis. Rare patients with restrictive atrial-level communications also benefit from a Rashkind balloon atrial septostomy (see Chapter 431.2) or surgical septectomy.

Infants with increased pulmonary blood flow because of an unobstructed pulmonary outflow tract (more often patients with aortopulmonary transposition) may require pulmonary arterial banding to decrease the symptoms of heart failure and protect the pulmonary bed from the development of pulmonary vascular disease. Infants with just adequate pulmonary blood flow who are well balanced between cyanosis and pulmonary overcirculation can be watched closely for the development of increasing cyanosis, which may occur as the VSD begins to get smaller or the pulmonary outflow becomes narrower and is an indication for surgery.

The next stage of palliation for patients with tricuspid atresia involves the creation of an anastomosis between the superior vena cava and the pulmonary arteries (bidirectional Glenn shunt; Fig. 430-9A). This procedure is performed at usually between 3 and 6 mo of age. The benefit of the Glenn shunt is that it reduces the volume load on the left ventricle and may lessen the chance of left ventricular dysfunction developing later in life.

The modified Fontan operation is the preferred approach to later surgical management. It is usually performed between 1.5 and 3 yr of age, usually after the patient is ambulatory. Initially, this procedure was performed by anastomosing the right atrium or atrial appendage directly to the pulmonary artery. The most commonly used procedure today is a modification of the Fontan procedure, known as a cavopulmonary isolation procedure, which involves anastomosing the inferior vena cava to the pulmonary arteries, either via a baffle that runs along the lateral wall of the right atrium (lateral tunnel Fontan; see Fig. 430-9B) or via a homograft or Gore-Tex tube running outside the heart (external conduit Fontan). The advantage of these later approaches is that blood flows by a more direct route into the pulmonary arteries, thereby decreasing the possibility of right atrial dilation and markedly reducing the incidence of postoperative pleural effusions, which were
common with the earlier method. In a completed Fontan repair, desaturated blood flows from both venae cavae directly into the pulmonary arteries. Oxygenated blood returns to the left atrium, enters the left ventricle, and is ejected into the systemic circulation. The volume load is completely removed from the left ventricle, and the right-to-left shunt is abolished. Because of the reliance on passive filling of the pulmonary circulation, the Fontan procedure is contraindicated in patients with elevated pulmonary vascular resistance, in those with pulmonary artery hypoplasia, and in patients with left ventricular dysfunction. The patient must also not have significant mitral insufficiency. Patients who are not in normal sinus rhythm are at increased risk and if a pacemaker is required in these patients, dual chamber pacing is the preferred approach.

Postoperative problems after the Fontan procedure include marked elevation of systemic venous pressure, fluid retention, and pleural or pericardial effusions. In the past, pleural effusions were a problem in 30-40% of patients using the standard Fontan procedure, but the cavopulmonary isolation procedure now in use reduces this risk to approximately 5%. Some centers use a fenestration at the time of the Fontan, consisting of a small communication between the inferior vena cava and the pulmonary artery conduit and the left atrium. This serves as a “pop-off” during early postoperative recovery and may hasten hospital discharge. The fenestration will result in some amount of right-to-left shunting, and is therefore usually closed with a catheter closure device after the immediate postoperative period.

Late complications of the Fontan procedure include baffle obstruction causing superior or inferior vena cava syndrome, vena cava or pulmonary artery thromboembolism, protein-losing enteropathy, plastic bronchiolitis, supraventricular arrhythmias (atrial flutter, paroxysmal atrial tachycardia), and hepatic cirrhosis (and possibly hepatic carcinoma) as a result of persistently elevated central venous pressures. Oral budesonide or sildenafil has been used with varying success to treat protein losing enteropathy associated with the Fontan procedure. Oral budesonide or sildenafil has been used with varying success to treat protein losing enteropathy associated with the Fontan procedure.

The 2-dimensional echocardiogram demonstrates both great vessels arising from the right ventricle and mitral-aortic valve discontinuity. The relationships between the aorta and pulmonary artery to the VSD can be delineated, and the presence of either pulmonary obstruction or aortic obstruction can be evaluated. Cardiac catheterization is not necessarily required if the echocardiogram is straightforward. Angiography will show that the aortic and pulmonary valves lie in the same horizontal plane and that both arise predominantly or exclusively from the right ventricle.

Surgical correction depends on the relationship of the great vessels to the VSD. If the VSD is subaortic, the repair may be similar to that used for tetralogy of Fallot, or consist of creating an intraventricular tunnel so that the left ventricle ejects blood through the VSD, into the tunnel, and into the aorta. The pulmonary obstruction is relieved either with an outflow patch or with a right ventricular to pulmonary artery homograft conduit (Rastelli operation). If the VSD is subpulmonic, the great vessels can be switched (see Chapter 430.6) and the Rastelli operation performed. However, if there is substantial aortic obstruction, or if 1 of the ventricles is hypoplastic, then a Norwood-style single-ventricle repair may be necessary (see Chapter 431.10). In small infants, palliation with an aortopulmonary shunt provides symptomatic improvement and allows for adequate growth before corrective surgery is performed.

**430.6 Transposition of the Great Arteries with Ventricular Septal Defect and Pulmonary Stenosis**

Daniel Bernstein

This combination of anomalies may mimic tetralogy of Fallot in its clinical features (see Chapter 430.1). However, because of the transposed great vessels, the site of obstruction is in the left as opposed to the right ventricle. The obstruction can be either valvular or subvalvular; the latter type may be dynamic, related to the interventricular septum or atrioventricular valve tissue, or acquired, as in patients with transposition and VSD after pulmonary arterial banding.

The age at which clinical manifestations initially appear varies from soon after birth to later infancy, depending on the degree of pulmonic stenosis. Clinical findings include cyanosis, decreased exercise tolerance, and poor physical development, similar to those described for tetralogy of Fallot; the heart is usually more enlarged. The pulmonary vasculature as seen on the roentgenogram is dependent on the degree of pulmonary obstruction. The electrocardiogram usually shows right axis deviation, right and left ventricular hypertrophy, and sometimes tall, spiked P waves. Echocardiography confirms the diagnosis and is useful in sequential evaluation of the degree and progression of the left ventricular outflow tract obstruction. Cardiac catheterization, if necessary, shows that pulmonary arterial pressure is low and that oxygen saturation in the pulmonary artery exceeds that in the aorta. Selective right and left ventriculography demonstrates the origin of the aorta from the right ventricle, the origin of the pulmonary artery from the left ventricle, the VSD, and the site and severity of the pulmonary stenosis.

An infusion of prostaglandin E$_1$, (0.01-0.20 µg/kg/min) should be started in neonates who present with cyanosis. When necessary, balloon atrial septostomy is performed to improve atrial-level mixing and to decompress the left atrium (see Chapter 431.2). Cyanotic infants may be palliated with an aortopulmonary shunt (see Chapter 430.1) followed by a Rastelli operation when older as the preferred corrective procedure. The Rastelli procedure achieves physiologic and anatomic correction by (1) closure of the VSD using an interventricular tunnel so that left ventricular blood flow is directed to the aorta, and (2) connection of the right ventricle to the pulmonary artery via an extracardiac homograft conduit between the right ventricle and the distal pulmonary artery (Fig. 430-10). These conduits will eventually become stenotic or functionally restrictive with growth of the patient and require replacement. Patients with milder degrees of pulmonary...
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Cyanotic Congenital Heart Lesions

Chapter 430◆Cyanotic Congenital Heart Lesions

and obstruction of the right ventricular outflow tract produced by the large, sail-like, anterior tricuspid valve leaflet. In newborns, right ventricular function may be so compromised that it is unable to generate enough force to open the pulmonary valve in systole, thus producing “functional” pulmonary atresia. Some infants have true anatomic pulmonary atresia. The increased volume of right atrial blood shunts through the foramen ovale (or through an associated atrial septal defect) to the left atrium and produces cyanosis (Fig. 430-11).

CLINICAL MANIFESTATIONS

The severity of symptoms and the degree of cyanosis are highly variable and depend on the extent of displacement of the tricuspid valve and the severity of right ventricular outflow tract obstruction. In many patients, symptoms are mild and may be delayed until the teenage years or young adult life; the patient may initially have fatigue or palpitations as a result of cardiac dysrhythmias. The atrial right-to-left shunt is responsible for cyanosis and polycythemia. Jugular venous pulsations, an index of central venous pressure, may be normal or increased in those with tricuspid insufficiency. On palpation, the precordium is quiet. A holosystolic murmur caused by tricuspid regurgitation is audible over most of the anterior left side of the chest. A gallop rhythm is common and often associated with multiple clicks at the lower left sternal border. A scratchy diastolic murmur may also be heard at the left sternal border. This murmur may mimic a pericardial friction rub.

Newborns with severe forms of Ebstein anomaly have marked cyanosis, massive cardiomegaly, and long holosystolic murmurs. Death may result from cardiac failure, hypoxemia, and pulmonary hypoplasia, the result of severe long-standing intrauterine right atrial enlargement. Spontaneous improvement may occur in some neonates as pulmonary vascular resistance falls and improves the ability of the right ventricle to provide pulmonary blood flow. The majority are

### PATHOPHYSIOLOGY

Ebstein anomaly consists of downward displacement of an abnormal tricuspid valve into the right ventricle. The defect arises from failure of the normal process by which the tricuspid valve is separated from the right ventricular myocardium (see Chapter 420). The anterior cusp of the valve retains some attachment to the valve ring, but the other leaflets are adherent to the wall of the right ventricle. The right ventricle is thus divided into 2 parts by the abnormal tricuspid valve: the first, a thin-walled “atrialized” portion, is continuous with the cavity of the right atrium; the second, often smaller portion consists of normal ventricular myocardium. The right atrium is enlarged as a result of tricuspid valve regurgitation, although the degree is extremely variable. In more severe forms of Ebstein anomaly, the effective output from the right side of the heart is decreased because of a combination of the poorly functioning small right ventricle, tricuspid valve regurgitation, and obstruction of the right ventricular outflow tract produced by the large, sail-like, anterior tricuspid valve leaflet. In newborns, right ventricular function may be so compromised that it is unable to generate enough force to open the pulmonary valve in systole, thus producing “functional” pulmonary atresia. Some infants have true anatomic pulmonary atresia. The increased volume of right atrial blood shunts through the foramen ovale (or through an associated atrial septal defect) to the left atrium and produces cyanosis (Fig. 430-11).

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Figure 430-11 Physiology of Ebstein anomaly of the tricuspid valve. Circled numbers represent oxygen saturation values. Inferior displacement of the tricuspid valve leaflets into the right ventricle has resulted in a thin-walled, low-pressure “atrialized” segment of right ventricle. The tricuspid valve is grossly insufficient (clear arrow). Right atrial blood flow is shunted right to left across an atrial septal defect or patent foramen ovale into the left atrium. Some blood may cross the right ventricular outflow tract and enter the pulmonary artery; however, in severe cases, the right ventricle may generate insufficient force to open the pulmonary valve, and “functional pulmonary atresia” results. In the left atrium, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected via the aorta. In this example, some pulmonary blood flow is derived from the right ventricle, the rest from a patent ductus arteriosus (PDA). Severe cyanosis will develop in neonates with a severe Ebstein anomaly when the PDA closes.

dependent on a PDA, and thus on a prostaglandin infusion, for pulmonary blood flow.

DIAGNOSIS

The electrocardiogram usually shows a right bundle-branch block without increased right precordial voltage, normal or tall and broad P waves, and a normal or prolonged P-R interval. Wolff-Parkinson-White syndrome (see Chapter 435) may be present and these patients may have episodes of supraventricular tachycardia. On radiographic examination, heart size varies from slightly enlarged to massive box-shaped cardiomegaly caused by enlargement of the right atrium. In newborns with severe Ebstein anomaly, the heart may totally obscure the pulmonary fields. Echocardiography is diagnostic and shows the degree of displacement of the tricuspid valve leaflets, a dilated right atrium, and any right ventricular outflow tract obstruction (Fig. 430-12). Pulsed and color Doppler examination demonstrates the degree of tricuspid regurgitation. In severe cases, the pulmonary valve may appear immobile and pulmonary blood flow may come solely from the ductus arteriosus. It may be difficult to distinguish true from functional pulmonary valve atresia. Cardiac catheterization, which is not usually necessary, confirms the presence of a large right atrium, an abnormal tricuspid valve, and any right-to-left shunt at the atrial level. The risk of arrhythmia is significant during catheterization and angiographic studies.

PROGNOSIS AND COMPLICATIONS

The prognosis in Ebstein anomaly is extremely variable and depends on the severity of the defect. The prognosis is more guarded for neonates or infants with intractable symptoms and cyanosis. Patients with milder degrees of Ebstein anomaly usually survive well into adult life.

There is an association of a form of left ventricular cardiomyopathy, isolated left ventricular noncompaction, in 18% of patients with Ebstein anomaly, and the severity of the left ventricular dysfunction directly impacts the prognosis.

TREATMENT

Neonates with severe hypoxia who are prostaglandin dependent have been treated with an aortopulmonary shunt alone, by repair of the tricuspid valve, or by surgical patch closure of the tricuspid valve, atrial septectomy, and placement of an aortopulmonary shunt (with eventual single ventricle repair using the Fontan procedure [see Chapter 430.4]). Many infants with Ebstein anomaly who have undergone valve repair will still have enough regurgitation that a Glenn shunt is performed to reduce the volume load on the right ventricle (see Chapter 430.4). In older children with mild or moderate disease, control of supraventricular dysrhythmias is of primary importance; surgical treatment may not be necessary until adolescence or young adulthood. In patients with severe tricuspid regurgitation, repair or replacement of the abnormal tricuspid valve along with closure of the atrial septal defect is carried out. In some older patients, a bidirectional Glenn shunt is also performed, with the superior vena cava anastomosed to the pulmonary arteries. This procedure reduces the volume of blood that the dysfunctional right side of the heart has to pump, thus creating a “one-and-one-half ventricle repair.”

Bibliography is available at Expert Consult.
Bibliography


431.1 D-Transposition of the Great Arteries

Transposition of the great vessels, a common cyanotic congenital anomaly, accounts for ≈5% of all congenital heart disease. In this anomaly, the systemic veins return normally to the right atrium and the pulmonary veins return to the left atrium. The connections between the atria and ventricles are also normal (atrioventricular concordance). The aorta arises from the right ventricle and the pulmonary artery from the left ventricle (Fig. 431-1). In normally related great vessels, the aorta is posterior and to the right of the pulmonary artery; in d-transposition of the great arteries (d-TGA), the aorta is anterior and to the right of the pulmonary artery (the d indicates a dextropositioned aorta, transposition indicates that it arises from the anterior right ventricle). Desaturated blood returning from the body to the right side of the heart goes inappropriately out the aorta and back to the body again, whereas oxygenated pulmonary venous blood returning to the left side of the heart is returned directly to the lungs. Thus, the systemic and pulmonary circulations exist as 2 parallel circuits. Survival in the immediate newborn period is provided by the foramen ovale and the ductus arteriosus, which permit some mixture of oxygenated and deoxygenated blood. Approximately 50% of patients with d-TGA also have a ventricular septal defect (VSD), which usually provides for better mixing. The clinical findings and hemodynamics vary in relation to the presence or absence of associated defects (e.g., VSD or pulmonary stenosis). d-TGA is more common in infants of diabetic mothers and in males (3:1). d-TGA, especially when accompanied by other cardiac defects such as pulmonic stenosis or right aortic arch, can be associated with deletion of chromosome 22q11.2 (DiGeorge syndrome [see Chapter 424]). Before the modern era of corrective or palliative surgery, mortality was >90% in the 1st yr of life.

431.2 D-Transposition of the Great Arteries with Intact Ventricular Septum

D-TGA with an intact ventricular septum is also referred to as simple TGA or isolated TGA. Before birth, oxygenation of the fetus is only slightly abnormal, but after birth, once the ductus arteriosus begins to close, the minimal mixing of systemic and pulmonary blood via the patent foramen ovale is usually insufficient and severe hypoxemia ensues, generally within the 1st few days of life.

CLINICAL MANIFESTATIONS
Cyanosis and tachypnea are most often recognized within the 1st hr or days of life. Untreated, the vast majority of these infants would not survive the neonatal period. Hypoxemia is usually moderate to severe, depending on the degree of atrial level shunting and whether the ductus is partially open or totally closed. This condition is a medical emergency, and only early diagnosis and appropriate intervention can avert the development of prolonged severe hypoxemia and acidosis, which lead to death. Physical findings, other than cyanosis, may be remarkably nonspecific. The precordial impulse may be normal, or a parasternal heave may be present. The 2nd heart sound is usually single and loud, although it may be split. Murmurs may be absent, or a soft systolic ejection murmur may be noted at the midleft sternal border.

DIAGNOSIS
The electrocardiogram is usually normal, showing the expected neonatal right-sided dominant pattern. Chest x-rays may show mild cardiomegaly, a narrow mediastinum (the classic “egg-shaped heart”), and normal to increased pulmonary blood flow. In the early newborn period, the chest roentgenogram is generally normal. As pulmonary vascular resistance drops during the 1st several wk of life, evidence of increased pulmonary blood flow becomes apparent. Arterial PO₂ is low and does not rise appreciably after the patient breathes 100% oxygen (hyperoxia test), although this test may not be totally reliable. Echocardiography is diagnostic and confirms the transposed ventricular-arterial connections (Fig. 431-2). The size of the interatrial communication and the ductus arteriosus can be visualized and the degree of mixing assessed by pulsed and color Doppler examination. The presence of any associated lesion, such as left ventricular outflow tract obstruction or a VSD, can also be assessed. The origins of the coronary arteries can be imaged, although echocardiography is generally not as accurate as catheterization for this purpose. Cardiac
TREATMENT

When transposition is suspected, an infusion of prostaglandin E1 should be initiated immediately to maintain patency of the ductus arteriosus and improve oxygenation (dosage: 0.01-0.20 µg/kg/min). Because of the risk of apnea associated with prostaglandin infusion, an individual skilled in neonatal endotracheal intubation should be available. Hypothermia intensifies the metabolic acidosis resulting from hypoxemia, and thus the patient should be kept warm. Prompt correction of acidosis and hypoglycemia is essential.

Infants who remain severely hypoxic or acidic despite prostaglandin infusion should undergo Rashkind balloon atrial septostomy (Fig. 431-3). A Rashkind atrial septostomy is also usually performed in all patients in whom any significant delay in surgery is necessary. If surgery is planned during the 1st 2 wk of life, the patient is stable, catheterization and atrial septostomy may be avoided.

A successful Rashkind atrial septostomy should result in a rise in Pao2 to 35-50 mm Hg and elimination of any pressure gradient across the atrial septum. Some patients with TGA and VSD (see Chapter 431.3) may require balloon atrial septostomy because of poor mixing, even though the VSD is large. Others may benefit from decompression of the left atrium to alleviate the symptoms of increased pulmonary blood flow and left-sided heart failure.

The arterial switch (Jatene) procedure is the surgical treatment of choice for neonates with d-TGA and an intact ventricular septum and is usually performed within the 1st 2 wk of life. The reason for this time frame is that as pulmonary vascular resistance declines after birth, catheterization may be performed in patients for whom noninvasive imaging is diagnostically inconclusive, where an unusual coronary artery anomaly is suspected, or in patients who require emergency balloon atrial septostomy (Rashkind procedure). Catheterization will show right ventricular pressure to be systemic because this ventricle is supporting the systemic circulation. The blood in the left ventricle and pulmonary artery has a higher oxygen saturation than that in the aorta. Depending on the age at catheterization, left ventricular and pulmonary arterial pressure can vary from systemic level to <50% of systemic level pressure. Right ventriculography demonstrates the anterior and rightward aorta originating from the right ventricle, as well as the intact ventricular septum. Left ventriculography shows that the pulmonary artery arises exclusively from the left ventricle.

Anomalous coronary arteries are noted in 10-15% of patients and defined by an aortic root injection or by selective coronary arteriography.

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The arterial switch procedure has a survival rate of >95% for uncomplicated d-TGA. It restores the normal physiologic relationships of systemic and pulmonary arterial blood flow and eliminates the long-term complications of the previously used atrial switch procedure.

Previous operations for d-TGA consisted of some form of atrial switch procedure (Mustard or Senning operation). These procedures produced excellent early survival (~85-90%), but had significant long-term morbidities. Atrial switch procedures reverse blood flow at the atrial level by the creation of an interatrial baffle that directs systemic venous blood returning from the vena cavae to the left atrium, where it will enter the left ventricle and then, via the pulmonary artery, the lungs. The same baffle also permits oxygenated pulmonary venous blood to cross over to the right atrium, right ventricle, and aorta. Atrial switch procedures involve significant atrial surgery and have been associated with the late development of atrial conduction disturbances, sick sinus syndrome with bradyarrhythmia and tachyarrhythmia, atrial flutter, sudden death, superior or inferior vena cava syndrome, edema, ascites, and protein-losing enteropathy. The atrial switch procedure also leaves the right ventricle as the systemic pumping chamber and these “systemic” right ventricles often begin to fail in young adulthood. Atrial
switch operations are currently reserved for patients whose anatomy is such that they are not candidates for the arterial switch procedure.

431.3 Transposition of the Great Arteries with Ventricular Septal Defect

If the VSD associated with d-TGA is small, the clinical manifestations, laboratory findings, and treatment are similar to those described previously for transposition with an intact ventricular septum. A harsh systolic murmur is audible at the lower left sternal border, resulting from flow through the defect. Many of these small defects eventually close spontaneously and may not be addressed at the time of surgery.

When the VSD is large and not restrictive to ventricular ejection, significant mixing of oxygenated and deoxygenated blood usually occurs and clinical manifestations of cardiac failure are seen. The degree of cyanosis may be subtle and sometimes may not be recognized until an oxygen saturation measurement is performed. The murmur is holosystolic and generally indistinguishable from that produced by a large VSD in patients with normally related great arteries. The heart is usually significantly enlarged.

Cardiomegaly, a narrow mediastinal waist, and increased pulmonary vascularity are demonstrated on the chest x-ray. The electrocardiogram shows prominent P waves and isolated right ventricular hypertrophy or biventricular hypertrophy. Occasionally, dominance of the left ventricle is present. Usually, the QRS axis is to the right, but it can be normal or even to the left. The diagnosis is confirmed by echocardiography, and the extent of pulmonary blood flow can also be assessed by the degree of enlargement of the left atrium and ventricle. In equivocal cases, the diagnosis can be confirmed by cardiac catheterization. Right and left ventriculography indicate the presence of arterial transposition and demonstrate the site and size of the VSD. Systolic pressure is equal in the 2 ventricles, the aorta, and the pulmonary artery. Left atrial pressure may be much higher than right atrial pressure, a finding indicative of a restrictive communication at the atrial level. At the time of cardiac catheterization, Rashkind balloon atrial septostomy may be performed to decompress the left atrium, even when adequate mixing is occurring at the ventricular level.

Surgical treatment is advised soon after diagnosis, because heart failure and failure to thrive are difficult to manage and pulmonary vascular disease can develop unusually rapidly in these patients. Preoperative management with diuretics lessens the symptoms of heart failure and stabilizes the patient prior to surgery.

Patients with d-TGA and a VSD without pulmonic stenosis can be treated with an arterial switch procedure combined with VSD closure. In these patients, the arterial switch operation can be safely performed after the 1st 2 wk of life because the VSD results in equal pressure in both ventricles and prevents regression of left ventricular muscle mass. At major centers, however, there is no reason to delay repair, as results are excellent whether the surgery is performed in the neonatal period or later.

431.4 L-Transposition of the Great Arteries (Corrected Transposition)

In l-transposition (l-TGA), the atroioventricular relationships are discordant: the right atrium is connected to the left ventricle and the left atrium to the right ventricle (also known as ventricular inversion). The great arteries are also transposed, with the aorta arising from the right ventricle and the pulmonary artery from the left. In contrast to d-TGA, the aorta arises to the left of the pulmonary artery (hence the designation l for levo-transposition). The aorta may be anterior to the pulmonary artery, although often they are nearly side by side.

The physiology of l-TGA is quite different from that of d-TGA. Desaturated systemic venous blood returns via the vena cavae to a normal right atrium, from which it passes through a bicuspid atroioventricular (mitral) valve into a right-sided ventricle that has the architecture and smooth wall morphologic features of the normal left ventricle (Fig. 431-5). Because transposition is also present, however, the desaturated blood ejected from this left ventricle enters the transposed pulmonary artery and flows into the lungs, as it would in the normal circulation. Oxygenated pulmonary venous blood returns to a normal left atrium, passes through a tricuspid atroioventricular valve into a left-sided ventricle, which has the trabeculated morphologic features of a normal right ventricle, and is then ejected into the...
transposed aorta. The double inversion of the atrioventricular and ventriculoarterial relationships result in desaturated right atrial blood appropriately flowing to the lungs and oxygenated pulmonary venous blood appropriately flowing to the aorta. The circulation is thus physiologically “corrected.” Without other defects, the hemodynamics would be nearly normal. In most patients, however, associated anomalies coexist: VSD, Ebstein-like abnormalities of the left-sided atrioventricular (tricuspid) valve, pulmonary valvular or subvalvular stenosis (or both), and atrioventricular conduction disturbances (complete heart block, accessory pathways such as Wolff-Parkinson-White syndrome).

**CLINICAL MANIFESTATIONS**

Symptoms and signs are widely variable and are determined by the associated lesions. If pulmonary outflow is unobstructed, the clinical signs are similar to those of an isolated VSD. If l-TGA is associated with pulmonary stenosis and a VSD, the clinical signs are more similar to those of tetralogy of Fallot.

**DIAGNOSIS**

The chest x-ray may suggest the abnormal position of the great arteries; the ascending aorta occupies the upper left border of the cardiac silhouette and has a straight profile. The electrocardiogram, in addition to atrioventricular conduction disturbances, may show abnormal P waves; absent Q waves in V\textsubscript{6}; abnormal Q waves in leads III, aVR, aVF, and V\textsubscript{1}; and upright T waves across the precordium. The echocardiogram is diagnostic. The characteristic echocardiographic features of the right ventricle (moderator band, coarse trabeculations, tricuspid valve that sits more inferiorly compared to the bicuspid mitral valve, and a smooth muscular conus or infundibulum separating the atrioventricular valve from the semilunar valve) allow the echocardiographer to determine the presence of atrioventricular discordance (right atrium connected to left ventricle; left atrium to right ventricle).

Surgical treatment of the associated anomalies, most often the VSD, is complicated by the position of the bundle of His, which can be injured at the time of surgery and result in heart block. Identification of the usual course of the bundle in corrected transposition (running superior to the defect) has been accomplished by mapping of the conduction system so that the surgeon can avoid the bundle of His during repair. Even without surgical injury, patients with l-TGA are at risk for heart block as they grow older.

Because simple surgical correction leaves the right ventricle as the systemic pumping chamber, and hence vulnerable to late ventricular failure, surgeons have become more aggressive about trying operations that utilize the left ventricle as the systemic pumping chamber. This is accomplished by performing an atrial switch operation, to reroute the systemic and pulmonary venous returns, in combination with an arterial switch operation to reroute the ventricular outflows (double switch procedure). The long-term benefit of this approach in preserving systemic ventricular function is still under investigation.

**Bibliography** is available at Expert Consult.

### 431.5 Double-Outlet Right Ventricle Without Pulmonary Stenosis

**Daniel Bernstein**

In double-outlet right ventricle without pulmonary stenosis, both the aorta and the pulmonary artery arise from the right ventricle (see Chapter 430.5). The only outlet from the left ventricle is through a VSD. In the absence of obstruction to pulmonary blood flow, clinical manifestations are similar to those of an uncomplicated VSD with a large left-to-right shunt, although mild systemic desaturation may be present because of mixing of oxygenated and deoxygenated blood in the right ventricle. The electrocardiogram usually shows biventricular hypertrophy. Echocardiography is diagnostic and shows the right ventricular origin of both great arteries, their anteroposterior relationship, as well as the relationship of the VSD to each of the great arteries. Surgical correction is dependent on these relationships. If the VSD is subaortic, it is accomplished by creation of an intracardiac tunnel. Blood is then ejected from the left ventricle via the VSD into the aorta. If the VSD is subpulmonic, an arterial switch may be performed in combination with an intracardiac tunnel. If pulmonary blood flow is excessive enough to cause congestive heart failure, pulmonary arterial banding may be required in infancy, followed by surgical correction when the child is bigger. When associated pulmonary stenosis is present, cyanosis is more marked, pulmonary blood flow is decreased, and clinical presentation may be similar to that of tetralogy of Fallot (see Chapter 430.5).

### 431.6 Double-Outlet Right Ventricle with Malposition of the Great Arteries (Taussig-Bing Anomaly)

**Daniel Bernstein**

In double-outlet right ventricle with malposed great arteries, the VSD is usually directly subpulmonary and the aorta distant from the left ventricle. Sometimes both the pulmonary and aortic valves may be located close to the VSD (doubly committed VSD) and sometimes neither is (doubly uncommitted VSD). The term malposition is used instead of transposition because both great arteries arise from the right ventricle. Aortic obstructive lesions are common, including valvular
Bibliography
and subvalvular aortic stenosis, coarctation of the aorta, and interruption of the aortic arch. Because pulmonary blood flow is unobstructed, patients experience cardiac failure early in infancy and are at risk for the development of pulmonary vascular disease and cyanosis. If aortic obstructive lesions are a component, patients can present with poor systemic output and cardiovascular collapse, particularly after the ductus begins to close. Cardiomegaly is usual, and a parasternal systolic ejection murmur is audible, sometimes preceded by an ejection click and loud closure of the pulmonary valve. The electrocardiogram shows right axis deviation and right, left, or biventricular hypertrophy. The chest x-ray shows cardiomegaly and prominence of the pulmonary vasculature. The anatomic features of the anomaly and associated abnormalities are usually demonstrated by echocardiography, augmented if necessary by either cardiac catheterization, MRI, or CT. Palliation may be achieved by pulmonary arterial banding in infancy and surgical correction at a later age, which may be accomplished by an arterial switch procedure (see Chapter 431.2) combined with an intracardiac baffle, or some modification of the Rastelli procedure (see Chapter 430.5).

### 431.7 Total Anomalous Pulmonary Venous Return

**Daniel Bernstein**

#### PATHOPHYSIOLOGY

Abnormal development of the pulmonary veins may result in either partial or complete anomalous drainage into the systemic venous circulation. Partial anomalous pulmonary venous return is usually an acyanotic lesion (see Chapter 426.4). Total anomalous pulmonary venous return (TAPVR) is associated with total mixing of systemic venous and pulmonary venous blood flow within the heart and thus produces cyanosis.

In TAPVR, the heart has no direct pulmonary venous connection into the left atrium. The pulmonary veins may drain above the diaphragm into the right atrium directly, into the coronary sinus, or into the superior vena cava via a "vertical vein," or they may drain below the diaphragm and join into a "descending vein" that enters into the inferior vena cava or one of its major tributaries, often via the ductus venosus. This latter form of anomalous venous drainage is most commonly associated with obstruction to venous flow, usually as the ductus venosus closes soon after birth, although supracardiac anomalous veins may also become obstructed. Occasionally, the drainage may be mixed, with some veins draining above and others below the diaphragm.

All forms of TAPVR involve mixing of oxygenated and deoxygenated blood before or at the level of the right atrium (total mixing lesion). This mixed right atrial blood either passes into the right ventricle and pulmonary artery or passes through an atrial septal defect (ASD) or patent foramen ovale into the left atrium, which will be the only source of systemic blood flow. The right atrium and ventricle and the pulmonary artery are generally enlarged, whereas the left atrium and ventricle may be normal or small. The clinical manifestations of TAPVR depend on the presence or absence of obstruction of the venous channels (Table 431-1). If pulmonary venous return is obstructed, severe pulmonary congestion and pulmonary hypertension develop; rapid deterioration occurs without surgical intervention. Obstructed TAPVR is a pediatric cardiac surgical emergency because prostaglandin therapy is usually not effective.

#### CLINICAL MANIFESTATIONS

Two major clinical patterns of TAPVR are seen, depending on the presence or absence of obstruction. Those neonates with severe obstruction to pulmonary venous return, most prevalent in the infracardiac group (see Table 431-1), present with severe cyanosis and respiratory distress. Murmurs may not be present. These infants are severely ill and fail to respond to mechanical ventilation. Rapid diagnosis and surgical correction are necessary for survival. In contrast, those with mild or no obstruction to pulmonary venous return are usually characterized by the development of heart failure as the pulmonary vascular resistance falls, with mild to moderate degrees of desaturation. Systolic murmurs may be audible along the left sternal border, and a gallop rhythm may be present. Some infants may have mild obstruction in the neonatal period and develop worsening obstruction as time passes.

#### DIAGNOSIS

The electrocardiogram demonstrates right ventricular hypertrophy (usually a qR pattern in V1 and V6, and the P waves are frequently tall and spiked). In neonates with marked pulmonary venous obstruction, the chest x-ray demonstrates a very dramatic perihilar pattern of pulmonary edema and a small heart. This appearance can sometimes be confused with primary pulmonary disease and the differential diagnosis includes persistent pulmonary hypertension of the newborn, respiratory distress syndrome, pneumonia (bacterial, meconium aspiration), pulmonary lymphangiectasia, and other heart defects (hypoplastic left heart syndrome). In older children, if the anomalous pulmonary veins enter the innominate vein and persistent left superior vena cava (Fig. 431-6), a large supracardiac shadow can be seen, which together with the normal cardiac shadow forms a “snowman” appearance. In most cases without obstruction, the heart is enlarged, the pulmonary artery and right ventricle are prominent, and pulmonary vascularization is increased.

The echocardiogram demonstrates a large right ventricle and usually identifies the pattern of abnormal pulmonary venous connections (Fig. 431-7). The demonstration of any vein with Doppler flow away from the heart is pathognomonic of TAPVR as normal venous flow is usually toward the heart. Shunting occurs from right to left at the atrial level. The size of the left atrium and left ventricle can be measured and the presence of any associated cardiac defects determined.

Echocardiography should be adequate to demonstrate TAPVR in most cases; however, if there is question about the drainage of 1 or more pulmonary veins, cardiac catheterization, MRI, or CT is performed. Catheterization shows that the oxygen saturation of blood in both atria, both ventricles, and the aorta is similar, indicative of a total mixing lesion. An increase in systemic venous saturation occurs at the site of entry of the abnormal pulmonary venous channel, either above or below the diaphragm. In older patients, pulmonary arterial and right ventricular pressure may be only moderately elevated, but in infants with pulmonary venous obstruction, pulmonary hypertension is usual. Selective pulmonary arteriography shows the anatomy of the pulmonary veins and their point of entry into the systemic venous circulation.

#### TREATMENT

Surgical correction of TAPVR is indicated during infancy, with emergent repair performed for those patients with venous obstruction. If

<table>
<thead>
<tr>
<th>Table 431-1</th>
<th>Total Anomalous Pulmonary Venous Return</th>
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<tr>
<td>SITE OF CONNECTION (% OF CASES)</td>
<td>% WITH SIGNIFICANT OBSTRUCTION</td>
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<td>Infra cardiac (20)</td>
<td>95-100</td>
</tr>
<tr>
<td>Mixed (5)</td>
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</tbody>
</table>

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**Chapter 431: Lesions Associated with Increased Pulmonary Blood Flow**
Part XX ♦ The Cardiovascular System

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Figure 431-7 Suprasternal 2-dimensional echocardiographic views demonstrating supracardiac total anomalous pulmonary venous return (type I). A, The large vertical ascending vein can be seen entering the innominate vein. There is a moderate narrowing where the anomalous vein enters the upper body venous system. B, Color Doppler examination shows a venous flow signal (red color) indicating that blood is moving away toward the transducer and thus from the heart (all venous flow should normally return toward the heart), diagnostic of anomalous pulmonary venous return. The turbulent acceleration of flow can be seen (arrow) where the vertical vein enters the innominate. Inn V, innominate vein; VV, vertical vein.

Figure 431-6 Chest x-ray of total anomalous pulmonary venous return to the left superior vena cava. A, Preoperative image. Arrows point to the supracardiac shadow, which produces the snowman or figure-8 configuration. Cardiomegaly and increased pulmonary vascularity are evident. B, Postoperative image showing a decrease in the size of the heart and the supracardiac shadow.

431.8 Truncus Arteriosus
Daniel Bernstein

PATHOPHYSIOLOGY
In truncus arteriosus, a single arterial trunk (truncus arteriosus) arises from the heart and supplies the systemic, pulmonary, and coronary circulations. A VSD is always present, with the truncus overriding the defect and receiving blood from both the right and left ventricles (Fig. 431-8). The number of truncal valve cusps varies from 2 to as many as 6 and the valve may be stenotic, regurgitant, or both. The pulmonary arteries can arise together from the posterior left side of the persistent truncus arteriosus and then divide into left and right pulmonary arteries (type I). In types II and III truncus arteriosus, no main pulmonary artery is present, and the right and left pulmonary arteries arise from separate orifices on the posterior (type II) or lateral (type III) aspects of the truncus arteriosus. Type IV truncus is a term no longer used because, in this case, there is no identifiable connection between the heart and pulmonary arteries, and pulmonary blood flow is derived from major aortopulmonary collateral arteries arising from the transverse or descending aorta; this is essentially a form of pulmonary atresia (see Chapter 430.2).

Both ventricles are at systemic pressure and both eject blood into the truncus. When pulmonary vascular resistance is relatively high immediately after birth, pulmonary blood flow may be normal; as pulmonary resistance drops in the 1st mo of life, blood flow to the lungs is greatly increased and heart failure ensues. Truncus arteriosus is a total mixing lesion with complete admixture of pulmonary and systemic venous return. Because of the large volume of pulmonary

surgery cannot be performed urgently, extracorporeal membrane oxygenation may be required to maintain oxygenation. Surgically, the pulmonary venous confluence is anastomosed directly to the left atrium, the ASD is closed, and any connection to the systemic venous circuit is interrupted. Early results are generally good, even for critically ill neonates. The postoperative period may be complicated by pulmonary vascular hypertensive crises. In some patients, especially those in whom the diagnosis was delayed or the obstruction was severe, recurrent stenosis and development of pulmonary veno-occlusive disease may occur. Attempts have been made to treat recurrent stenosis with surgery, balloon angioplasty, stents, and antiproliferative chemotherapy. To date, the long-term prognosis in these patients is very guarded and in those with aggressive veno-occlusive disease, heart-lung transplantation may be the only option (see Chapter 443.2).

Bibliography is available at Expert Consult.
Bibliography
blood flow, clinical cyanosis is usually mild. If the lesion is left untreated, pulmonary resistance eventually increases, pulmonary blood flow decreases, and cyanosis becomes more prominent (Eisenmenger physiology; see Chapter 433.2).

CLINICAL MANIFESTATIONS
The clinical signs of truncus arteriosus vary with age and depend on the level of pulmonary vascular resistance. In the immediate newborn period, signs of heart failure are usually absent; a murmur and minimal cyanosis may be the only initial findings. Over the next 1-2 mo of life, pulmonary blood flow begins to become torrential and the clinical picture is dominated by heart failure, with still mild cyanosis. Runoff of blood from the truncus to the pulmonary circulation may result in a wide pulse pressure and bounding pulses. These findings will be further exaggerated if truncal valve insufficiency is present. The heart is usually enlarged, and the precordium is hyperdynamic. The 2nd heart sound is loud and single. A systolic ejection murmur, sometimes accompanied by a thrill, is generally audible along the left sternal border. The murmur is frequently preceded by an early systolic ejection click due to the abnormal truncal valve. In the presence of truncal valve insufficiency, a high-pitched early diastolic decrescendo murmur is heard at the mid-left sternal border. An apical mid-diastolic rumbling murmur caused by increased flow through the mitral valve is often audible with the bell of the stethoscope, especially as heart failure develops. Truncus arteriosus is a conotruncal malformation and may be associated with DiGeorge syndrome, linked to a deletion of a large region of chromosome 22q11 (see Chapter 424).

DIAGNOSIS
The electrocardiogram shows right, left, or combined ventricular hypertrophy. The chest x-ray also shows considerable variation. Cardiac enlargement will develop over the 1st several wk of life, and is a result of the prominence of both ventricles. The truncus may produce a prominent shadow that follows the normal course of the ascending aorta and aortic knob; the aortic arch is right-sided in 50% of patients. Sometimes a high bulge left of the aortic knob is produced by the main or left pulmonary artery. Pulmonary vascularity is increased after the 1st few wk of life. Echocardiography is diagnostic and demonstrates the large truncal valve overriding the ventricular septal defect. In this case, only the left pulmonary artery (LPA) arises from the truncus (TR). The pulmonary arteries are discontinuous and the right pulmonary artery arises from the descending aorta via the ductus arteriosus (not shown). Ao, aorta; LV, left ventricle; RV, right ventricle.

PROGNOSIS AND COMPLICATIONS
Surgical results have been excellent, and many patients with repaired truncus are now entering adulthood. The need to replace the right ventricular to pulmonary artery conduit as the child grows means that these patients will need to undergo multiple operations by the time they reach adulthood. When truncus arteriosus is associated with DiGeorge syndrome, the associated endocrine, immunologic, craniofacial, and airway abnormalities may complicate recovery.

TREATMENT
In the 1st few wk of life, many of these infants can be managed with anticoagulant medications; as pulmonary vascular resistance falls, heart failure symptoms worsen and surgery is indicated, usually within the 1st few mo. Delay of surgery much beyond this time period may increase the likelihood of pulmonary vascular disease; many centers now perform routine neonatal repair at the time of diagnosis. At surgery, the VSD is closed, the pulmonary arteries are separated from the truncus, and continuity is established between the right ventricle and the pulmonary arteries with a homograft conduit. Immediate surgical results are excellent, but these conduits will develop either regurgitation or stenosis over time, and must be replaced, often several times, as the child grows. If regurgitation is the primary problem, patients can now be treated with a transcatheter stent-valve.

Bibliography is available at Expert Consult.

431.9 Single Ventricle (Double-Inlet Ventricle, Univentricular Heart)
Daniel Bernstein

PATHOPHYSIOLOGY
With a single ventricle, both atria empty through a common atrioventricular valve or via 2 separate valves into a single ventricular chamber, with total mixing of systemic and pulmonary venous return. This
Bibliography
chamber may have left, right, or indeterminate ventricular anatomic characteristics. The aorta and pulmonary artery both arise from this single chamber, although one of the great vessels may originate from a rudimentary outflow chamber. The aorta may be posterior, anterior (malposition), or side by side with the pulmonary artery and either to the right or to the left. Pulmonary stenosis or atresia is common.

### CLINICAL MANIFESTATIONS

The clinical picture is variable and depends on the associated intracardiac anomalies. If pulmonary outflow is obstructed, the findings are usually similar to those of tetralogy of Fallot: marked cyanosis without heart failure. If pulmonary outflow is unobstructed, the findings are similar to those of transposition with VSD: minimal cyanosis with increasing heart failure.

In patients with **pulmonary stenosis**, cyanosis is present in early infancy. Cardiomegaly is mild or moderate, a left parasternal lift is palpable, and a systolic thrill is common. The systolic ejection murmur is usually loud; an ejection click may be audible, and the 2nd heart sound is single and loud. In patients with **unobstructed pulmonary flow**, as pulmonary vascular resistance drops, torrential pulmonary blood flow develops, and these patients present with tachypnea, dyspnea, failure to thrive, and recurrent pulmonary infections. Cyanosis is only mild or moderate. Cardiomegaly is generally marked, and a left parasternal lift is palpable. A systolic ejection murmur is present but is not usually loud or harsh, and the 2nd heart sound is loud and closely split. A 3rd heart sound is common and may be followed by a short mid-diastolic rumbling murmur caused by increased flow through the atrioventricular valves. The eventual development of pulmonary vascular disease reduces pulmonary blood flow so that the cyanosis increases and signs of cardiac failure appear to improve (Eisenmenger physiology; see Chapter 433.2).

### DIAGNOSIS

Findings on the electrocardiogram are nonspecific. P waves are normal, spiked, or bifid. The precordial lead pattern suggests right ventricular hypertrophy, combined ventricular hypertrophy, or sometimes left ventricular dominance. The initial QRS forces are usually to the left and anterior. Radiographic examination confirms the degree of cardiomegaly. If present, a rudimentary outflow chamber may produce a bulge on the upper left border of the cardiac silhouette in the postero-anterior projection. In the absence of pulmonary stenosis, pulmonary vasculature is increased, whereas in the presence of pulmonary stenosis, pulmonary vasculature is diminished. Echocardiography will confirm the absence or near absence of the ventricular septum and can usually determine whether the single ventricle has right, left, or mixed morphologic features. The presence of a rudimentary outflow chamber under one of the great vessels can be identified, and pulsed Doppler can be used to determine whether flow through this communication (known as a *bulboventricular foramen*) is obstructed.

If cardiac catheterization is performed, the pressure in the single ventricular chamber is at systemic level; however, a gradient may be demonstrated across the entrance to a rudimentary outflow chamber. Pressure measurements and angiography demonstrate whether pulmonary stenosis is present.

### PROGNOSIS AND COMPLICATIONS

Unoperated, some patients succumb during infancy from heart failure. Others may survive to adolescence and early adult life but finally succumb to the effects of chronic hypoxemia or, in the absence of pulmonary stenosis, to the effects of pulmonary vascular disease. Patients with moderate pulmonary stenosis have the best prognosis because pulmonary blood flow, though restricted, is still adequate. Surgical palliation, eventually leading to Fontan-type circulatory physiology (see Chapter 430.4), has very good short- and intermediate-term results.

### TREATMENT

If pulmonary stenosis is severe, a Blalock-Taussig aortopulmonary shunt is performed to provide a reliable source of pulmonary blood flow (see Chapter 430.1). If pulmonary blood flow is unrestricted, pulmonary arterial banding is used to control heart failure and prevent progressive pulmonary vascular disease. The **bidirectional Glenn shunt** is usually performed at between 2 and 6 mo of age, followed by a modified Fontan operation (cavopulmonary isolation procedure; see Chapter 430.4) at 2-3 yr of age. If subaortic stenosis is present because of a restrictive connection to a rudimentary outflow chamber, (restrictive bulboventricular foramen) surgical relief can be provided by anastomosing the proximal pulmonary artery to the side of the ascending aorta (Damus-Stansel-Kaye operation).

### 431.10 Hypoplastic Left-Heart Syndrome

**Daniel Bernstein**

#### PATHOPHYSIOLOGY

The term *hypoplastic left heart* is used to describe a related group of anomalies that include various degrees of underdevelopment of the left side of the heart: stenosis or atresia of the aortic and mitral valves and hypoplasia of the left ventricular cavity and ascending aorta. Two broad categories include aortic atresia with hypoplastic but perforate mitral valve or with mitral atresia. The left ventricle may be only moderately hypoplastic, very small and nonfunctional, or totally atretic; in the immediate neonatal period the right ventricle maintains both the pulmonary circulation and the systemic circulation via the ductus arteriosus (Fig. 431-10). Pulmonary venous blood passes through an ASD or dilated foramen ovale from the left to the right side of the heart, where it mixes with systemic venous blood (total mixing lesion).

Figure 431-10 Physiology of hypoplastic left-heart syndrome (HLHS). Circled numbers represent oxygen saturation values. HLHS is not a single lesion but a constellation of different degrees of hypoplasia of the left-sided heart structures. This drawing shows a patent mitral valve, a small left ventricular cavity, and a diminutive ascending aorta. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Desaturated blood enters the right atrium, flows through the tricuspid valve into the right ventricle, and is ejected into the pulmonary artery. Because of the markedly decreased left ventricular compliance, most of the pulmonary venous blood returning to the left atrium shunts left to right at the atrial level. A small amount of left atrial blood will cross the mitral valve and be ejected into the tiny ascending aorta. The right ventricular oxygen saturation represents a mixing of desaturated systemic venous blood and saturated pulmonary venous blood. Pulmonary artery blood flows into the pulmonary arteries as well as left to right across the patent ductus arteriosus (PDA) into the aorta. Ductal blood flows grade to the descending aorta as well as retrograde to the ascending aorta, where it supplies the head and neck vessels in addition to the coronary arteries (which arise off the small ascending aorta). Closure of the PDA results in profound hypoxia and circulatory collapse.
When the ventricular septum is intact, which is usually the case, all the right ventricular blood is ejected into the main pulmonary artery; the descending aorta is supplied via the ductus arteriosus, and flow from the ductus also fills the ascending aorta and coronary arteries in a retrograde fashion. The major hemodynamic abnormalities are inadequate maintenance of the systemic circulation and, depending on the size of the atrial-level communication, either pulmonary venous hypertension (restrictive foramen ovale) or pulmonary overcirculation (moderate or large ASD).

**CLINICAL MANIFESTATIONS**

Although cyanosis may not always be obvious in the 1st 48 hr of life, a grayish-blue color of the skin is soon apparent and denotes a mix of cyanosis and poor perfusion. The condition is diagnosed in most infants in the 1st few hr or days of life. Once the ductus arteriosus begins to close, signs of poor systemic perfusion and shock predominate. All of the peripheral pulses may be weak or absent. A palpable right ventricular parasternal lift may be present along with a non-inspiratory systolic murmur.

This lesion may be isolated or associated in 5-15% of patients with known genetic syndromes, such as Turner syndrome, trisomy 13, 18, or 21, Jacobsen syndrome (11q deletion), Holt-Oram syndrome, and Robinow-Taybi syndrome. In these circumstances, noncardiac manifestations of the syndrome may be evident and influence the clinical outcomes. Occasionally it is familial and inherited as an autosomal recessive trait.

**DIAGNOSIS**

On the chest x-ray, the heart is variable in size in the 1st days of life, but cardiomegaly develops rapidly and is associated with increased pulmonary vascularity. The initial electrocardiogram may show only the normal neonatal pattern of right ventricular dominance, but later, P waves become prominent and right ventricular hypertrophy is usual with reduced left ventricular forces. The echocardiogram is diagnostic and demonstrates absence or hypoplasia of the mitral valve and aortic root, a variably small left atrium and left ventricle, and a large right atrium and right ventricle (Fig. 431-11). The size of the atrial communication, by which pulmonary venous blood leaves the left atrium, can be assessed directly and by pulsed and color flow Doppler studies. The small ascending aorta and transverse aortic arch are identified and the best reported results demonstrate a 90-95% survival rate. If a Norwood or Sano procedure is to be performed, preoperative medical management includes correction of acidosis and hypoglycemia, maintenance of ductus arteriosus patency with prostaglandin E1 (0.01-0.20 µg/kg/min) to support systemic blood flow, and prevention of hypothermia. Preoperative management should avoid excessive pulmonary blood flow; either through management of ventilator settings, increasing the concentration of inspired CO2, or decreasing the concentration of inspired O2. Balloon dilation of the atrial septum may be indicated.

The Norwood procedure is usually performed in 3 stages. **Stage I** (see Fig. 431-12) includes an atrial septectomy and transection and ligation of the distal main pulmonary artery; the proximal pulmonary arterial arch is then connected to the transversely opened hypoplastic aortic arch to form a neo-aorta, extending through the coarcted segment of the juxtaductal aortic arch. A synthetic aortopulmonary (Blalock-Taussig) shunt connects the aorta to the main pulmonary artery to provide controlled pulmonary blood flow. In the Sano modification, a right ventricle to pulmonary artery conduit is used instead of an aortopulmonary shunt to provide pulmonary blood flow, temporarily creating a double-outlet right ventricle. The operative risk for these 1st-stage procedures has improved dramatically in the past 2 decades and the best reported results demonstrate a 90-95% survival rate.

**Stage II** consists of a Glenn anastomosis to connect the superior vena cava to the pulmonary arteries (see Chapter 431.4), at between 2 and 6 mo of age. **Stage III**, usually performed at 2-3 yr of age, consists of a modified Fontan procedure (cavopulmonary isolation) to connect the inferior vena cava to the pulmonary arteries via either an intratrial or external baffle. After stage III, all systemic venous return enters the pulmonary circulation directly. Pulmonary venous flow enters the left atrium and is directed across the atrial septum to the tricuspid valve and subsequently to the right (now the systemic) ventricle. Blood leaves the right ventricle via the neo-aorta, which supplies the systemic cardiac catheterization. If catheterization is necessary, the hypoplastic ascending aorta is demonstrated by angiography.

**PROGNOSIS AND COMPLICATIONS**

Untreated patients most often succumb during the 1st few mo of life, usually during the 1st or 2nd wk. Occasionally, unoperated patients may live for months or, rarely, years. Up to 30% of infants with hypoplastic left-heart syndrome have evidence of either a major or minor central nervous system abnormality. Other dysmorphic features may be found in up to 40% of patients. Thus, careful preoperative evaluation (genetic, neurologic, ophthalmologic) should be performed in patients being considered for surgical therapy.

Intermediate-term follow up after completion of all 3 stages of the Norwood procedure demonstrates generally good exercise capacity, and complications equivalent to other patients who have had the Fontan palliation (see Chapter 430.4). Some studies show that patients with hypoplastic left-heart syndrome have a higher risk of neurodevelopmental problems than those with other complex congenital heart lesions. Whether the poor neurodevelopmental outcome is due to prenatal associated central nervous system injury or malformation, the alterations of cerebral hemodynamics during bypass surgery, or poor postoperative perfusion is unknown. In addition, poor outcome is associated with prematurity, chromosome syndromes, and poverty.

**TREATMENT**

Surgical therapy for hypoplastic left-heart syndrome is associated with improving survival rates, reported as high as 90-95% for the 1st-stage palliation in experienced centers. The 1st-stage repair is designed to construct a reliable source of systemic blood flow arising from the single right ventricle using a combination of aortic and pulmonary arterial tissue, and to limit pulmonary blood flow to avoid heart failure and prevent the development of pulmonary vascular disease. The 2 surgical procedures most commonly utilized are the Norwood procedure (Fig. 431-12) and the Sano procedure. Primary heart transplantation, previously advocated by a few centers, is much less common because of the substantially improved survival rates with standard surgery and the limited supply of donor organs in this age group.

If a Norwood or Sano procedure is to be performed, preoperative medical management includes correction of acidosis and hypoglycemia, maintenance of ductus arteriosus patency with prostaglandin E1 (0.01-0.20 µg/kg/min) to support systemic blood flow, and prevention of hypothermia. Preoperative management should avoid excessive pulmonary blood flow; either through management of ventilator settings, increasing the concentration of inspired CO2, or decreasing the concentration of inspired O2. Balloon dilation of the atrial septum may be indicated.
The Norwood procedure, 1 of the 2 current techniques for 1st-stage palliation of hypoplastic left-heart syndrome. 

**A**, Incisions used for the procedure incorporate a cuff of arterial wall allograft. The distal divided main pulmonary artery may be closed by direct suture or with a patch. 

**B**, Dimensions of the cuff of the arterial wall allograft. 

**C**, The arterial wall allograft is used to supplement the anastomosis between the proximal divided main pulmonary artery and the ascending aorta, aortic arch, and proximal descending aorta. 

**D** and **E**, The procedure is completed by an atrial septectomy and a 3.5-mm modified right Blalock shunt. 

**F**, When the ascending aorta is particularly small, an alternative procedure involves placement of a complete tube of arterial allograft. The tiny ascending aorta may be left in situ, as indicated, or implanted into the side of the neo-aorta. 

circulation. The old aortic root now attached to the neoartery provides coronary blood flow. The risks associated with stages II and III are even less than those of stage I; interstage mortality (usually between stages I and II) has been reduced with the use of home monitoring programs. The short- and long-term benefits of using the Norwood versus the Sano procedure remain to be demonstrated.

An alternative therapeutic approach is to perform a hybrid procedure for the 1st stage. This involves performing a Rashkind balloon atrial septostomy, catheter placement of a stent in the ductus arteriosus, and surgical placement of bilateral pulmonary artery bands. After the hybrid procedure, patients can be weaned off prostaglandin and discharged from hospital. After the hybrid procedure, patients need to undergo a more extensive 2nd-stage procedure involving construction of a neoartery and removal of the pulmonary artery bands.

Another alternative therapy is cardiac transplantation, either in the immediate neonatal period, thereby obviating stage I of the Norwood procedure, or after a successful stage I Norwood procedure is performed as a bridge to transplantation. After transplantation, patients usually have normal cardiac function and no symptoms of heart failure; however, these patients have the chronic risk of organ rejection and lifelong immunosuppressive therapy (see Chapter 443.1). The combination of donor shortage and improved results with standard surgical and hybrid procedures has caused most centers to stop recommending transplantation except when associated lesions make the Norwood operation an exceptionally high-risk procedure, or for patients who develop poor ventricular function at some time after the standard surgical approach.

There are some subgroups of patients with hypoplastic left-heart syndrome that may be at increased surgical risk, particularly those with mitral stenosis plus aortic atresia. These data need confirmation in larger studies, and alternative approaches to remain to be developed.

**PREVENTION**

Serial fetal echocardiographic studies demonstrate that in some fetuses, hypoplastic left-heart syndrome may be a progressive lesion, beginning with simple valvar aortic stenosis in midgestation. The decreased flow through the stenotic aortic valve reduces flow through the left ventricle during development, resulting in gradual ventricular chamber hypoplasia. The potential for preventing this hypoplasia has been demonstrated by performing in utero aortic balloon valvuloplasty in midgestation fetuses (Fig. 431-13). Early results are encouraging, although even if the aortic valve is successfully opened, adequate ventricular growth occurs in only about 30% of patients. At present, this procedure is regarded as experimental.

**Bibliography is available at Expert Consult.**

### 431.11 Abnormal Positions of the Heart and the Heterotaxy Syndromes (Asplenia, Polysplenia)

Daniel Bernstein

Classification and diagnosis of abnormal cardiac position are best performed via a segmental approach, with the position of the viscera and atria defined first, and then the ventricles, followed by the great vessels (Fig. 431-14). Determination of viscerocardiocentric situs can be made by radiography demonstration of the position of the abdominal organs and the tracheal bifurcation for recognition of the right and left bronchi and by echocardiography. The atrial situs is usually similar to the situs of the viscera and lungs. In situs solitus, the viscera are in their normal positions (stomach and spleen on the left, liver on the right), the
Bibliography


3-lobed right lung is on the right, and the 2-lobed left lung on the left; the right atrium is on the right, and the left atrium is on the left. When the abdominal organs and lung lobation are reversed, an arrangement known as situs inversus occur, the left atrium is on the right and the right atrium on the left. If the viscerotrautal situs cannot be readily determined, a condition known as situs indeterminus or heterotaxia exists. The 2 major variations are (1) asplenia syndrome (right isomerism or bilateral left-sidedness), which is associated with a centrally located liver, absent spleen, and 2 morphologic right lungs (Fig. 431-15); and (2) polysplenia syndrome (left isomerism or bilateral left-sidedness), which is associated with multiple small spleens, absence of the intrahepatic portion of the inferior vena cava, and 2 morphologic left lungs (Fig. 431-16). The heterotaxia syndromes are usually associated with severe congenital heart lesions: ASD, VSD, atrioventricular septal defect, hypoplasia of 1 of the ventricles, pulmonary stenosis or atresia, and anomalous systemic venous or pulmonary venous return (Table 431-2).

The next segment is localization of the ventricles, which depends on the direction of development of the embryonic cardiac loop. Initial protrusion of the loop to the right (d-loop) carries the future right ventricle anteriorly and to the right, whereas the left ventricle remains posterior and on the left. With situs solitus, a d-loop yields normal atrioventricular connections (right atrium connecting to the right ventricle, left atrium to the left ventricle). Protrusion of the loop to the left (l-loop) carries the future right ventricle to the left and the left ventricle to the right. In this case, in the presence of situs solitus, the right atrium connects with the left ventricle and the left atrium with the right ventricle (ventricular inversion).

The final segment is that of the great vessels. With each type of cardiac loop, the ventricular-arterial relationships may be regarded as either normal (right ventricle to the pulmonary artery, left ventricle to the aorta) or transposed (right ventricle to the aorta, left ventricle to the pulmonary artery). A further classification can be based on the position of the aorta (normally to the right and posterior) relative to the pulmonary artery. In transposition, the aorta is usually anterior and either to the right of the pulmonary artery (d-transposition) or to the left (l-transposition). These segmental relationships can usually be determined by echocardiographic studies demonstrating both atrioventricular and ventriculoarterial relationships. The clinical manifestations of these syndromes of abnormal cardiac position are determined primarily by their associated cardiovascular anomalies.

Dextrocardia occurs when the heart is in the right side of the chest; levocardia (the normal situation) is present when the heart is in the left side of the chest. Dextrocardia without associated situs inversus and levocardia in the presence of situs inversus are most often complicated by other severe cardiac malformations. Surveys of older children and adults indicate that dextrocardia with situs inversus and normally related great arteries ("mirror-image" dextrocardia) is often associated with a functionally normal heart, although congenital heart disease of a less severe nature is common.

Anatomic or functional abnormalities of the lungs, diaphragm, and thoracic cage may result in displacement of the heart to the right (dextraposition). In this case, however, the cardiac apex is pointed...
### Table 431-2  Comparison of Cardiosplenic Heterotaxy Syndromes

<table>
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<th>FEATURE</th>
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</tr>
<tr>
<td>Right-sided stomach</td>
<td>Yes</td>
<td>Less common</td>
</tr>
<tr>
<td>Symmetric liver</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Partial intestinal rotation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dextrocardia (%)</td>
<td>30-40</td>
<td>30-40</td>
</tr>
<tr>
<td>Pulmonary blood flow</td>
<td>Decreased (usually)</td>
<td>Increased (usually)</td>
</tr>
<tr>
<td>Severe cyanosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Transposition of great arteries (%)</td>
<td>60-75</td>
<td>15</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return (%)</td>
<td>70-80</td>
<td>Rare</td>
</tr>
<tr>
<td>Common atroventricular valve (%)</td>
<td>80-90</td>
<td>20-40</td>
</tr>
<tr>
<td>Single ventricle (%)</td>
<td>40-50</td>
<td>10-15</td>
</tr>
<tr>
<td>Absent inferior vena cava with azygos continuation</td>
<td>No</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Bilateral superior vena cava</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Other common defects</td>
<td>PA, PS</td>
<td>Partial anomalous pulmonary venous return, ventricular septal defect, double-outlet right ventricle</td>
</tr>
<tr>
<td>Risk of pneumococcal sepsis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Howell-Jolly and Heinz bodies, pitted erythrocytes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk of nosocomial infection</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Absent gallbladder; biliary atresia</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PA, pulmonary atresia; PS, pulmonary stenosis.

normally to the left. This anatomic position is less often associated with congenital heart lesions, although hypoplasia of a lung may be accompanied by anomalous pulmonary venous return from that lung (scimitar syndrome [see Chapter 426.4]).

The electrocardiogram is difficult to interpret in the presence of lesions with discordant atrial, ventricular, and great vessel anatomy. Diagnosis usually requires detailed echocardiographic and sometimes MRI, CT, or cardiac catheterization studies. The prognosis and treatment of patients with 1 of the cardiac positional anomalies are determined by the underlying defects and are covered in their respective chapters. Asplenia increases the risk of serious infections such as bacterial sepsis and thus requires daily antibiotic prophylaxis. Patients with polysplenia frequently have poor splenic function and may also require prophylaxis against pneumococcal sepsis. Patients with heterotaxia are also at increased risk of intestinal malrotation and volvulus.

Bibliography is available at Expert Consult.
Bibliography


Chapter 432 Other Congenital Heart and Vascular Malformations

432.1 Anomalies of the Aortic Arch

Daniel Bernstein

RIGHT AORTIC ARCH

In this abnormality, the aorta curves to the right and, if it descends on the right side of the vertebral column, is usually associated with other cardiac malformations. It is found in 20% of cases of tetralogy of Fallot and is also common in truncus arteriosus. A right aortic arch without other cardiac anomalies is not associated with symptoms. It can often be visualized on the chest roentgenogram. The trachea is deviated slightly to the left of the midline rather than to the right, as in the presence of a normal left arch. On a barium esophagogram, the esophagus is indented on its right border at the level of the aortic arch.
Congenital abnormalities of the aortic arch and its major branches result in the formation of vascular rings around the trachea and esophagus with varying degrees of compression (Table 432-1). The origin of these lesions can best be appreciated by reviewing the embryology of the aortic arch (see Fig. 420-1 in Chapter 420). The most common anomalies include (1) double aortic arch (Fig. 432-1A), (2) right aortic arch with a left ligamentum arteriosum, (3) anomalous innominate artery arising farther to the left on the arch than usual, (4) anomalous left carotid artery arising farther to the right than usual and passing anterior to the trachea, and (5) anomalous left pulmonary artery (vascular sling). In the latter anomaly, the abnormal vessel arises from an elongated main pulmonary artery or from the right pulmonary artery. It courses between and compresses the trachea and the esophagus. Associated congenital heart disease may be present in 5-50% of patients, depending on the vascular anomaly.

**Clinical Manifestations**
If the vascular ring produces compression of the trachea and esophagus, symptoms are frequently present during infancy. Chronic wheezing is exacerbated by crying, feeding, and flexion of the neck. Extension of the neck tends to relieve the noisy respiration. Vomiting may also be a component. Affected infants may have a brassy cough, pneumonia, or rarely, sudden death from aspiration.

**Diagnosis**
Standard roentgenographic examination is not usually helpful. In the past, performing a barium esophagogram was the standard method of diagnosis (Fig. 432-2), replaced today by echocardiography in combination with either MRI or CT. Cardiac catheterization is reserved for cases with associated anomalies or in rare cases where these other modalities are not diagnostic. Bronchoscopy may be helpful in more severe cases to determine the extent of airway narrowing.

**Treatment**
Surgery is advised for symptomatic patients who have evidence of tracheal compression. The anterior vessel is usually divided in patients with a double aortic arch (see Fig. 432-1B). Compression produced by a right aortic arch and left ligamentum arteriosum is relieved by division of the latter. Anomalous innominate or carotid arteries cannot be

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**Table 432-1**  Vascular Rings

<table>
<thead>
<tr>
<th>LESION</th>
<th>SYMPTOMS</th>
<th>PLAIN FILM</th>
<th>BARIUM SWALLOW</th>
<th>BRONCHOSCOPY</th>
<th>MRI ECHOCARDIOGRAPHY</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOUBLE ARCH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stridor</td>
<td>Respiratory distress</td>
<td>AP—wider</td>
<td>Bilateral tracheal</td>
<td>Diagnostic</td>
<td>Ligate and divide smaller</td>
</tr>
<tr>
<td></td>
<td>Swallowing dysfunction</td>
<td></td>
<td>base of heart</td>
<td>indentation of both</td>
<td></td>
<td>arch (usually left)</td>
</tr>
<tr>
<td></td>
<td>Reflex apnea</td>
<td>Lat.—narrowed trachea displaced</td>
<td>Lat.—</td>
<td>pulsatile</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>forward at C3-C4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RIGHT ARCH AND LIGAMENTUM/DUCTUS</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
<td>Swallowing dysfunction</td>
<td>AP—tracheal</td>
<td>Bilateral tracheal</td>
<td>Diagnostic</td>
<td>Ligate ligamentum or ductus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>deviation to</td>
<td>compression—r. pulsatile</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>left (right arch)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>ANOMALOUS INNOMINATE</strong></td>
<td>Cough</td>
<td>Stridor</td>
<td>AP—normal</td>
<td>Pulsatile anterior tracheal</td>
<td>Unnecessary</td>
<td>Conservative apnea, then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reflex apnea</td>
<td>Lat.—</td>
<td>tracheal compression</td>
<td></td>
<td>suspend</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>anterior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ABERRANT RIGHT SUBCLAVIAN</strong></td>
<td>Occasional swallowing</td>
<td>Normal</td>
<td>AP—oblique</td>
<td>Usually normal</td>
<td>Diagnostic</td>
<td>Ligate artery</td>
</tr>
<tr>
<td></td>
<td>dysfunction</td>
<td></td>
<td>defect upward</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>to right</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Lat.—small</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>defect on right</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>posterior wall</td>
<td></td>
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<tr>
<td><strong>PULMONARY SLING</strong></td>
<td>Expiratory stridor</td>
<td>Respiratory distress</td>
<td>AP—low L.</td>
<td>Tracheal displacement to left</td>
<td>Diagnostic</td>
<td>Detach and reanastomose to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hilum, r.</td>
<td></td>
<td></td>
<td>main pulmonary artery in front of trachea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>emphysema/</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>atelectasis</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Lat.—</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>anterior</td>
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<td></td>
<td></td>
<td></td>
<td>indentation</td>
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<td></td>
<td></td>
<td></td>
<td>above carina</td>
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<td>between</td>
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<td></td>
<td></td>
<td></td>
<td>esophagus and</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>trachea</td>
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<td></td>
</tr>
</tbody>
</table>

AP, anteroposterior; L and I., left; Lat., lateral; MRI, magnetic resonance imaging; R and r., right.

in blood flow; congenital heart diseases include coarctation of the aorta, supravalvular aortic stenosis, aortic regurgitation, pulmonary atresia with intact ventricular septum, hypoplastic left-heart syndrome, and coronary ectasia secondary to cyanotic heart disease.

**ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY**

In anomalous origin of the left coronary artery from the pulmonary artery, the blood supply to the left ventricular myocardium is severely compromised. Soon after birth, as pulmonary arterial pressure falls, perfusion pressure to the left coronary artery becomes inadequate; myocardial ischemia, infarction, and fibrosis result. In some cases, interarterial collateral anastomoses develop between the right and left coronary arteries. Blood flow in the left coronary artery is then reversed, and it empties into the pulmonary artery, a condition known as the “myocardial steal” syndrome. The left ventricle becomes dilated, and its performance is decreased. Mitral insufficiency is a frequent complication secondary to a dilated valve ring or infarction of a papillary muscle. Localized aneurysms may also develop in the left ventricular free wall. Occasional patients have adequate myocardial blood flow during childhood and, later in life, a continuous murmur and a small left-to-right shunt via the dilated coronary system (aorta to right coronary to left coronary to pulmonary artery).
Bibliography
Part XX  The Cardiovascular System

Table 432-2  Congenital Anomalies of Coronary Arteries Unassociated with Congenital Heart Disease

<table>
<thead>
<tr>
<th>Anomalous Aortic Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eccentric ostium within an aortic sinus</td>
</tr>
<tr>
<td>Ectopic ostium above an aortic sinus</td>
</tr>
<tr>
<td>Conus artery from the right aortic sinus</td>
</tr>
<tr>
<td>Circumflex coronary artery from the right aortic sinus or from the right coronary artery</td>
</tr>
<tr>
<td>Origin of left anterior descending and circumflex coronary arteries from separate ostia in the left aortic sinus (absence of left main coronary artery)</td>
</tr>
<tr>
<td>Atresia of the left main coronary artery</td>
</tr>
<tr>
<td>Origin of the left anterior descending coronary artery from the right aortic sinus or from the right coronary artery</td>
</tr>
<tr>
<td>Origin of the right coronary artery from the left aortic sinus, from posterior aortic sinus, or from left coronary artery</td>
</tr>
<tr>
<td>Origin of a single coronary artery from the right or left aortic sinus</td>
</tr>
<tr>
<td>Anomalous origin from a noncardiac systemic artery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anomalous Aortic Origin with Anomalous Proximal Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute proximal angulation</td>
</tr>
<tr>
<td>Ectopic right coronary artery passing between aorta and pulmonary trunk</td>
</tr>
<tr>
<td>Ectopic left main coronary artery:</td>
</tr>
<tr>
<td>Between aorta and pulmonary trunk</td>
</tr>
<tr>
<td>Anterior to the pulmonary trunk</td>
</tr>
<tr>
<td>Posterior to the aorta</td>
</tr>
<tr>
<td>Within the ventricular septum (intramyocardial)</td>
</tr>
<tr>
<td>Ectopic left anterior descending coronary artery that is anterior, posterior, or between the aorta and pulmonary trunk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anomalous Origin of a Coronary Artery from the Pulmonary Trunk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main coronary artery</td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
</tr>
<tr>
<td>Right coronary artery</td>
</tr>
<tr>
<td>Both right and left coronary arteries</td>
</tr>
<tr>
<td>Circumflex coronary artery</td>
</tr>
<tr>
<td>Accessory coronary artery</td>
</tr>
</tbody>
</table>


Clinical Manifestations

Evidence of heart failure becomes apparent within the 1st few mo of life, and may be exacerbated by respiratory infection. Recurrent attacks of discomfort, restlessness, irritability, sweating, dyspnea, and pallor occur and probably represent angina pectoris. Cardiac enlargement is moderate to massive. A gallop rhythm is common. Murmurs may be of the nonspecific ejection type or may be holosystolic due to mitral insufficiency. Older patients with abundant intercoronary anastomoses may have continuous murmurs and minimal left ventricular dysfunc-


Anomalous Origin of the Right Coronary Artery from the Pulmonary Artery

Anomalous origin of the right coronary artery from the pulmonary artery is rarely manifested in infancy or early childhood. The left coronary artery is enlarged, whereas the right is thin-walled and mildly enlarged. In early infancy, perfusion of the right coronary artery is from the pulmonary artery, whereas later, perfusion is from collaterals of the left coronary vessels. Angina and sudden death can occur in adolescence or adulthood. When recognized, this anomaly should be repaired by re-anastomosis of the right coronary artery to the aorta.

ECTOPIC ORIGIN OF THE CORONARY ARTERY FROM THE AORTA WITH ABERRANT PROXIMAL COURSE

In ectopic origin of the coronary artery from the aorta with an aberrant proximal course, the aberrant artery may be a left, right, or major branch coronary artery. The site of origin may be the wrong sinus of Valsalva or a proximal coronary artery. The ostium may be hypoplastic, stiltlike, or of normal caliber. The aberrant vessel may pass anteriorly, posteriorly, or between the aorta and right ventricular outflow tract; it may tunnel in the conal or interventricular septal tissue. Obstruction is diagnostic; aortography shows immediate opacification of the right coronary artery only. This vessel is large and tortuous. After filling of the intercoronary anastomoses, the left coronary artery is opacified, and contrast can be seen to enter the pulmonary artery. Pulmonary arteriography may also opacify the origin of the anomalous left coronary artery. Selective left ventriculography usually demonstrates a dilated left ventricle that empties poorly and mitral regurgitation.

Treatment and Prognosis

Untreated, death often occurs from heart failure within the 1st 6 mo of life. Those who survive generally have abundant intercoronary collateral anastomoses. Medical management includes standard therapy for heart failure (diuretics, angiotensin-converting enzyme inhibitors) and for controlling ischemia (nitrates, β-blocking agents).

Surgical treatment consists of detaching the anomalous coronary artery from the pulmonary artery and anastomosing it to the aorta to establish normal myocardial perfusion. A seriously ill infant with a tiny left coronary artery may present a difficult technical problem. In patients who have already sustained a significant myocardial infarction, cardiac transplantation may be the best option (see Chapter 441.1).

Figure 432-3  Electrocardiogram of a 3 mo old child with anomalous origin of the left coronary artery from the pulmonary artery. Lateral myocardial infarction is present as evidenced by abnormally large and wide Q waves in leads I, V₅, and V₆; an elevated ST segment in V₅ and V₆; and inversion of TV₆.
resulting from hypoplasia of the ostia, tunneling between the aorta and right ventricular outflow tract or interventricular septum, and acute angulation produces myocardial infarction. Unobstructed vessels produce no symptoms. Patients with this extremely rare abnormality are often initially seen with severe myocardial infarction, ventricular arrhythmias, angina pectoris, or syncope; sudden death may occur, especially in young athletes.

Diagnostic modalities include an electrocardiogram, stress testing, 2-dimensional echocardiography, CT or MRI, radionuclide perfusion scan, and cardiac catheterization with selective coronary angiography.

Treatment is indicated for obstructed vessels and consists of aorto-pulmonary resection and reanastomosis of the aberrant vessel or, occasionally, coronary artery bypass grafting. The management of asymptomatic infants with these forms of ectopic coronary origin remains controversial.

Bibliography is available at Expert Consult.

432.3 Pulmonary Arteriovenous Fistula

Daniel Bernstein

Fistulous vascular communications in the lungs may be large and localized or multiple, scattered, and small. The most common form of this unusual condition is the Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia type I), which is also associated with angiomas of the nasal and buccal mucous membranes, gastrointestinal tract, or liver. Mutations in the endoglin gene, a cell surface component of the transforming growth factor-β receptor complex, cause this syndrome. The usual communication is between the pulmonary artery and pulmonary vein; direct communication between the pulmonary artery and left atrium is extremely rare. Desaturated blood in the pulmonary artery is shunted through the fistula into the pulmonary vein, thus bypassing the lungs, and then enters the left side of the heart resulting in systemic arterial desaturation and, sometimes, clinically detectable cyanosis. The shunt across the fistula is at low pressure and resistance, so pulmonary arterial pressure is normal; cardiomegaly and heart failure are not present.

The clinical manifestations depend on the magnitude of the shunt. Large fistulas are associated with dyspnea, cyanosis, clubbing, a continuous murmur, and polycythemia. Hemoptysis is rare, but when it occurs, it may be massive. Features of the Osler-Weber-Rendu syndrome are seen in 50% of patients (or other family members) and include recurrent epistaxis and gastrointestinal tract bleeding. Transitory dizziness, diplopia, aphasia, motor weakness, or convulsions may result from cerebral thrombosis, abscess, or paradoxical emboli. Soft systolic or continuous murmurs may be audible over the site of the fistula. The electrocardiogram is normal. Roentgenographic examination of the chest may show opacities produced by large fistulas; multiple small fistulas may be visualized by fluoroscopy (as abnormal pulsations), MRI, or CT. Selective pulmonary arteriography demonstrates the site, extent, and distribution of the fistulas.

Treatment consisting of excision of solitary or localized lesions by lobectomy or wedge resection results in complete disappearance of symptoms. In most instances, fistulas are so widespread that surgery is not possible. Any direct communication between the pulmonary artery and the left atrium can be obliterated.

Patients who have undergone a Glenn cavopulmonary anastomosis for cyanotic congenital heart disease (see Chapter 430.4) are also at risk for the development of pulmonary arteriovenous malformations. In these patients, the arteriovenous malformations are usually multiple and the risk increases over time after the Glenn procedure. These malformations rarely occur after the heart disease is fully palliated by completion of the Fontan operation. This finding suggests that the pulmonary circulation requires an as yet undetermined hepatic factor to suppress the development of arteriovenous malformations. The hallmark of the development of these malformations is a decrease in the patient’s oxygen saturation. The diagnosis can often be made with contrast echocardiography; cardiac catheterization is the definitive test. Completion of the Fontan circuit, so that inferior vena cava blood flow (containing hepatic venous drainage) is routed through the lungs, usually results in improvement or resolution of the malformations.

Bibliography is available at Expert Consult.

432.4 Ectopia Cordis

Daniel Bernstein

In the most common thoracic form of ectopia cordis, the sternum is split and the heart protrudes outside the chest. In other forms, the heart protrudes through the diaphragm into the abdominal cavity or may be situated in the neck. Associated intracardiac anomalies are common. Pentalogy of Cantrell consists of ectopia cordis, midline supraumbilical abdominal defect, deficiency of the anterior diaphragm, defect of the lower sternum, and an intracardiac defect (either a ventricular septal defect, tetralogy of Fallot, or diverticulum of the left ventricle). Death may occur early in life, usually from infection, cardiac failure, or hypoxemia. Surgical therapy for neonates without overwhelmingly severe cardiac anomalies consists of covering the heart with skin without compromising venous return or ventricular ejection. Repair or palliation of associated defects is also necessary.

432.5 Diverticulum of the Left Ventricle

Daniel Bernstein

Left ventricular diverticulum is a rare anomaly, where the diverticulum protrudes into the epigastrium. The lesion may be isolated or associated with complex cardiovascular anomalies. A pulsating mass is usually visible and palpable in the epigastrium. Systolic or systolic-diastolic murmurs produced by blood flow into and out of the diverticulum may be audible over the lower part of the sternum and the mass. The electrocardiogram shows a pattern of complete or incomplete left bundle branch block. Roentgenograms of the chest may or may not show the mass. Associated abnormalities include defects of the sternum, abdominal wall, diaphragm, and pericardium (see earlier). Surgical treatment of the diverticulum and associated cardiac defects can be performed in selected cases. Occasionally, a diverticulum may be small and not associated with clinical symptoms. These small diverticula are diagnosed at the time of echocardiographic examination for other indications.
Bibliography


Bibliography


Chapter 433  Pulmonary Hypertension

433.1 Primary Pulmonary Hypertension
Daniel Bernstein

PATHOPHYSIOLOGY
Primary pulmonary hypertension is characterized by pulmonary vascular obstructive disease and right-sided heart failure. It occurs at any age, although in pediatric patients the mean age at diagnosis is 7-10 yr. In patients with idiopathic or familial disease, females outnumber males 1.7:1; in other patients, both genders are represented equally. Some patients have evidence of either an immunologic disorder or a hypercoagulable state. Mutations in the gene for bone morphogenetic protein receptor-2 (BMPR-2, a member of the transforming growth factor-β receptor family) on chromosome 2q33 have been identified in 70% of patients with familial primary pulmonary hypertension (known as 

PPH1) and in 10-20% with idiopathic sporadic pulmonary
hypertension. Other potential disease causing genes include PPH2, ALK1, ENG, SMAD9, CAV1, and KCNK3, which causes a channelopathy in familial and sporadic cases of primary pulmonary hypertension. Viral infection, such as with the vasculotropic human herpesvirus 8, has been suggested as a trigger factor in many patients. Diet pills, particularly fenfluramine, have also been implicated. Pulmonary hypertension is a common complication of sickle cell anemia and other hemolytic anemias. Pulmonary hypertension is associated with precapillary obstruction of the pulmonary vascular bed as a result of hyperplasia of the muscular and elastic tissues and a thickened intima of the small pulmonary arteries and arterioles (Fig. 433-1). Secondary atherosclerotic changes may be found in the large pulmonary arteries as well. In children, pulmonary venoocclusive disease may account for some cases of primary pulmonary hypertension. Before a diagnosis of primary pulmonary hypertension can be made, other causes of elevated pulmonary arterial pressure must be eliminated (chronic pulmonary parenchymal disease, persistent obstruction of the upper airway, congenital cardiac malformations, recurrent pulmonary emboli, alveolar capillary dysplasia, liver disease, autoimmune disease, and moyamoya disease). Table 433-1 provides a classification system. Idiopathic or familial disease is the most common in pediatric patients (~55%), followed by pulmonary hypertension secondary to congenital heart disease (~35%) and chronic respiratory disorders (~15%).

Pulmonary hypertension places an afterload burden on the right ventricle, which results in right ventricular hypertrophy. Dilation of the pulmonary artery is present, and pulmonary valve insufficiency may occur. In the later stages of the disease, the right ventricle dilates, tricuspid insufficiency develops, and cardiac output is decreased. Arrhythmias, syncope, and sudden death are common.

**CLINICAL MANIFESTATIONS**

The predominant symptoms include exercise intolerance (dyspnea) and fatigability; occasionally, precordial chest pain, dizziness, or headaches are noted. Syncope may be noted in ~30% of pediatric patients. Peripheral cyanosis may be present, especially during exercise or in patients with a patent foramen ovale through which blood can shunt from right to left; in the late stages of disease, patients may have cold extremities and a gray appearance associated with low cardiac output. Arterial oxygen saturation is usually normal unless there is an associated intracardiac shunt. If right-sided heart failure has supervened, jugular venous pressure is elevated, and hepatomegaly and edema are present. Jugular venous a waves are present, and in those with functional tricuspid insufficiency, a conspicuous jugular cv wave and systolic hepatic pulsations are manifested. The heart is moderately enlarged, and a right ventricular heave can be noted. The 1st heart sound is often followed

![Figure 433-1 Vascular abnormalities associated with pulmonary arterial hypertension: abnormal muscularization of distal and medial precapillary arteries, loss of precapillary arteries, thickening of large pulmonary arteries, and neoimal formation that is occlusive in vessels <500-100 µM and in plexiform lesions therein. (From Rabino-vitch M: Molecular pathogenesis of pulmonary arterial hypertension. J Clin Invest 122:4306-4313, 2012, Fig. 1.)](image)

**Table 433-1 Revised World Health Organization Classification of Pulmonary Hypertension**

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension (PAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1. Idiopathic (IPAH)</td>
</tr>
<tr>
<td>1.2. Familial (FPAH)</td>
</tr>
<tr>
<td>1.3. Associated with (PAH):</td>
</tr>
<tr>
<td>1.3.1. Connective tissue disorder</td>
</tr>
<tr>
<td>1.3.2. Congenital systemic-to-pulmonary shunts</td>
</tr>
<tr>
<td>1.3.3. Portal hypertension</td>
</tr>
<tr>
<td>1.3.4. HIV infection</td>
</tr>
<tr>
<td>1.3.5. Drugs and toxins</td>
</tr>
<tr>
<td>1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)</td>
</tr>
<tr>
<td>1.4. Associated with significant venous or capillary involvement</td>
</tr>
<tr>
<td>1.4.1. Pulmonary venoocclusive disease (PVOD)</td>
</tr>
<tr>
<td>1.4.2. Pulmonary capillary hemangiomatosis (PCH)</td>
</tr>
<tr>
<td>1.5. Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>2. Pulmonary hypertension with left-heart disease</td>
</tr>
<tr>
<td>2.1. Left-sided atrial or ventricular heart disease</td>
</tr>
<tr>
<td>2.2. Left-sided valvular heart disease</td>
</tr>
<tr>
<td>3. Pulmonary hypertension associated with lung diseases and/or hypoxemia</td>
</tr>
<tr>
<td>3.1. Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>3.2. Interstitial lung disease</td>
</tr>
<tr>
<td>3.3. Sleep disordered breathing</td>
</tr>
<tr>
<td>3.4. Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>3.5. Chronic exposure to high altitude</td>
</tr>
<tr>
<td>3.6. Developmental abnormalities</td>
</tr>
<tr>
<td>4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)</td>
</tr>
<tr>
<td>4.1. Thromboembolic obstruction of proximal pulmonary arteries</td>
</tr>
<tr>
<td>4.2. Thromboembolic obstruction of distal pulmonary arteries</td>
</tr>
<tr>
<td>4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)</td>
</tr>
<tr>
<td>5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)</td>
</tr>
</tbody>
</table>

Pulmonary Hypertension

**Fig. 433-2 A**, X-ray from a 3 yr old girl with primary pulmonary hypertension. Pulmonary vascularity is reduced. The pulmonary trunk (PT), right atrium (RA), and right ventricle (RV) are considerably enlarged. **B**, Histology of an intrapulmonary artery at necropsy shows medial hypertrophy (arrow). (From Perloff JK, Marelli AJ: Perloff’s clinical recognition of congenital heart disease, ed 6, Philadelphia, 2012, Elsevier/Saunders, Fig. 14-17, p. 207.)

by an ejection click emanating from the dilated pulmonary artery. The 2nd heart sound is narrowly split, loud, and sometimes booming in quality; it is frequently palpable at the upper left sternal border. A presystolic gallop rhythm may be audible at the lower left sternal border. The systolic murmur is short and soft and is sometimes followed by a blowing decrescendo diastolic murmur caused by pulmonary insufficiency. In later stages, a holosystolic murmur of tricuspid insufficiency is appreciated at the lower left sternal border.

**DIAGNOSIS**

Chest radiographs reveal a prominent pulmonary artery and right ventricle (Fig. 433–2). The pulmonary vascularity in the hilar areas may be prominent, in contrast to the peripheral lung fields in which pulmonary markings are decreased. The electrocardiogram shows right ventricular hypertrophy, often with spiked P waves. Echocardiography is used to screen for any congenital cardiac malformations. Doppler evaluation of the tricuspid valve, if insufficiency is present, will allow estimation of the right ventricular (and hence pulmonary arterial) systolic pressure.

At cardiac catheterization, the presence of left-sided obstructive lesions (pulmonary venous stenosis, mitral stenosis, restrictive cardiomyopathy) that result in pulmonary venous hypertension can be evaluated (see Chapters 427.9, 431.7, and 439.3). The presence of pulmonary arterial hypertension with a normal pulmonary capillary wedge pressure is diagnostic of primary pulmonary hypertension. If the wedge pressure is elevated and left ventricular end-diastolic pressure is normal, obstruction at the level of the pulmonary veins, left atrium, or mitral valve should be suspected. If left ventricular end-diastolic pressure is also elevated, the diagnosis of restrictive cardiomyopathy should be entertained. The risks associated with cardiac catheterization are increased in severely ill patients with primary pulmonary hypertension.

**PROGNOSIS AND TREATMENT**

Primary pulmonary hypertension is progressive, and no cure is currently available. Some success has been reported with oral calcium channel blocking agents such as nifedipine in children who demonstrate pulmonary vasoreactivity when these agents are administered during catheterization. Continuous intravenous infusion of the arachidonic acid metabolite, prostacyclin (epoprostenol), provides relief as long as the infusion is continued. Despite the success of prostacyclin in reducing symptoms and improving quality of life, it slows but does not stop the progression of the disease. Treprostinil, a prostacyclin analog with a longer half-life has also been shown to be effective. Continuous administration of nitric oxide via nasal cannula, nebulized forms of prostacyclin (iloprost), and orally administered pulmonary vasodilators (bosentan, an antagonist of endothelin receptors; or sildenafil, a phosphodiesterase type 5 inhibitor) have been used with success in adults and in preliminary clinical studies in children (Table 433-2). Anticoagulation may be of value in patients with previous pulmonary thromboemboli; some of these patients may respond to balloon angioplasty of narrowed pulmonary artery segments. Riociguat, a soluble guanylate cyclase stimulator, with vasorelaxation, antiproliferation, and antifibrotic properties, has proven effective in adults with chronic thromboembolic or idiopathic pulmonary hypertension. Despite many advances, definitive therapy is still heart-lung or lung transplantation (see Chapter 443.2). In patients with severe pulmonary hypertension and low cardiac output, the terminal event is often sudden and related to a lethal arrhythmia. Patients with primary pulmonary hypertension diagnosed in infancy often have rapid progression and high mortality.

**433.2 Pulmonary Vascular Disease**

**Eisenmenger Syndrome**

Daniel Bernstein

**PATHOPHYSIOLOGY**

The term Eisenmenger syndrome refers to patients with a ventricular septal defect in which blood is shunted partially or totally from right to left as a result of the development of pulmonary vascular disease. This physiologic abnormality can also occur with atrioventricular septal defect, ventricular septal defect, patent ductus arteriosus or any other communication between the aorta and pulmonary artery, and in many forms of complex congenital heart disease with unrestricted pulmonary blood flow. Pulmonary vascular disease with an isolated atrial septal defect can occur, but is less common and does not occur until late in adulthood.

In Eisenmenger syndrome, pulmonary vascular resistance after birth either remains high or, after having decreased during early infancy, rises thereafter because of increased shear stress on pulmonary arterioles. Factors playing a role in the rapidity of development of pulmonary vascular disease include increased pulmonary arterial pressure, increased pulmonary blood flow, and the presence of hypoxia or hypercapnia. Early
in the course of disease, pulmonary hypertension (elevated pressure in the pulmonary arteries) is the result of markedly increased pulmonary blood flow (hyperkinetic pulmonary hypertension). This form of pulmonary hypertension decreases with the administration of pulmonary vasodilators such as nitric oxide, or oxygen, or both. With the development of Eisenmenger syndrome, pulmonary hypertension is the result of pulmonary vascular disease (obstructive pathologic changes in the pulmonary arteries) is the result of markedly increased pulmonary blood flow (hyperkinetic pulmonary hypertension). This form of pulmonary hypertension decreases with the administration of pulmonary vasodilators such as nitric oxide, or oxygen, or both. With the development of Eisenmenger syndrome, pulmonary hypertension is the result of pulmonary vascular disease (obstructive pathologic changes in the pulmonary arteries). This form of pulmonary hypertension is usually only minimally responsive to pulmonary vasodilators or oxygen or not at all.

**PATHOLOGY AND PATHOPHYSIOLOGY**

The pathologic changes of Eisenmenger syndrome occur in the small pulmonary arterioles and muscular arteries (<300 µm) and are graded on the basis of histologic characteristics (Heath-Edwards classification): Grade I changes involve medial hypertrophy alone, grade II consists of medial hypertrophy and intimal hyperplasia, grade III involves near obliteration of the vessel lumen, grade IV includes arterial dilation, and grades V and VI includeplexiform lesions, angiomatoid formation, and fibrinoid necrosis. Grades IV-VI indicate irreversible pulmonary vascular obstructive disease. Eisenmenger physiology is usually defined by an absolute elevation in pulmonary arterial resistance to greater than 12 Wood units (resistance units indexed to body surface area) or by a ratio of pulmonary to systemic vascular resistance of ≥1.0.

Pulmonary vascular disease occurs more rapidly in patients with trisomy 21 who have left-to-right shunts. It also complicates the natural history of patients with elevated pulmonary venous pressure secondary to mitral stenosis or left ventricular dysfunction, especially in those patients with restrictive cardiomyopathy (see Chapter 445.3). Pulmonary vascular disease can also occur in any patient with transmission of systemic pressure to the pulmonary circulation via a shunt at the interventricular or great vessel level, and in patients chronically exposed to low Po2 (because of high altitude). Patients with cyanotic congenital heart lesions associated with unrestricted pulmonary blood flow are at particularly high risk.

**CLINICAL MANIFESTATIONS**

Symptoms do not usually develop until the 2nd or 3rd decade of life, although a more fulminating course may occur. Intracardiac or extracardiac communications that would normally shunt from left to right are converted to right-to-left shunting as pulmonary vascular resistance exceeds systemic vascular resistance. Cyanosis becomes apparent, and dyspnea, fatigue, and a tendency toward dysrhythmias begin to occur. In the late stages of the disease, heart failure, chest pain, headaches, syncope, and hemoptysis may be seen. Physical examination reveals a right ventricular heave and a narrowly split 2nd heart sound with a loud pulmonic component. Palpable pulmonary artery pulsation may be present at the left upper sternal border. A holosystolic murmur of tricuspid regurgitation may be audible along the left sternal border. An early decrescendo diastolic murmur of pulmonary insufficiency may also be heard along the left sternal border. The degree of cyanosis depends on the stage of the disease.

**DIAGNOSIS**

Roentgenographically, the heart varies in size from normal to greatly enlarged; the latter usually occurs late in the course of the disease. The main pulmonary artery is generally prominent, similar to primary pulmonary hypertension (see Fig. 433-2). The pulmonary vessels are enlarged in the hilar areas and taper rapidly in caliber in the peripheral branches. The right ventricle and atrium are prominent. The electrocardiogram shows marked right ventricular hypertrophy. The P wave may be tall and spiked. Cyanotic patients have various degrees of polycythemia that depend on the severity and duration of hypoxemia.

The echocardiogram shows a thick-walled right ventricle and demonstrates the underlying congenital heart lesion. Two-dimensional echocardiography assists in eliminating from consideration lesions such as obstructed pulmonary veins, supramitral membrane, mitral stenosis, and restrictive cardiomyopathy. Doppler studies demonstrate the direction of the intracardiac shunt and the presence of a typical hypertension waveform in the main pulmonary artery. Tricuspid and pulmonary regurgitation can be used in the Doppler examination to estimate pulmonary arterial systolic and diastolic pressures.

Cardiac catheterization usually shows a bidirectional shunt at the site of the defect. Systolic pressure is generally equal in the systemic and pulmonary circulations. Pulmonary capillary wedge pressure is normal unless a left-sided heart obstructive lesion or left ventricular failure is the cause of the pulmonary arterial hypertension. Arterial oxygen saturation is decreased depending on the magnitude of

**Table 433-2** Summary of Drugs Used to Treat Pulmonary Hypertension*

<table>
<thead>
<tr>
<th>DRUG AND MECHANISM OF ACTION</th>
<th>DOSES USED IN PEDIATRIC STUDIES</th>
<th>COMMON SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol (prostacyclin [PGL], a potent vasodilator, also inhibits platelet aggregation)</td>
<td>1 ng/kg/min initially. Increase based on clinical course and tolerance to 5-50 ng/kg/min. Some patients may require even higher doses. Must be given by continuous infusion that is not interrupted</td>
<td>Flushing, headache, nausea, diarrhea, hypotension, chest pain, jaw pain</td>
</tr>
<tr>
<td>Iloprost (synthetic analog of PGL)</td>
<td>2.5-5.0 µg 6-9 times daily (not more frequently than every 2 hr) via inhalation</td>
<td>Flushing, headache, diarrhea, hypotension, jaw pain, exacerbation of pulmonary symptoms (cough, wheezing)</td>
</tr>
<tr>
<td>Treprostinil (synthetic analog of PGL)</td>
<td>1 ng/kg/min initially. Target dose ranges from 20-80 ng/kg/min. Given either IV or SC via continuous infusion. Longer half-life than epoprostenol</td>
<td>Flushing, headache, diarrhea, hypotension, jaw pain. Pain at infusion site when given SC</td>
</tr>
<tr>
<td>Bosentan, ambrisentan, (endothelin receptor EtA and EtB antagonist)</td>
<td>2 mg/kg/dose bid. Use 1/2 dose for 1st mo and check for liver function test abnormalities prior to up-titrating</td>
<td>Flushing, headache, diarrhea, hypotension, fluid retention, exacerbation of heart failure, anemia, elevated liver function tests, palpitations</td>
</tr>
<tr>
<td>Sildenafil (inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase 5)</td>
<td>1 mg/kg/dose given 3-4 times daily. Initial dosing should be 1/2 final target dose to evaluate for hypotension</td>
<td>Flushing, headache, diarrhea, myalgia, hypotension, priapism, visual disturbance (blue coloration)</td>
</tr>
<tr>
<td>Calcium channel blockers (amlodipine, diltiazem, nifedipine)</td>
<td>Previously widely used. Now indicated only for patients who show a strong response to nitric oxide during cardiac catheterization</td>
<td>Flushing, headache, edema, arrhythmia, headache, hypotension, rash, nausea, constipation, elevated liver function tests</td>
</tr>
</tbody>
</table>

*These medications should only be administered under the direction of a specialist in pulmonary hypertension.
the right-to-left shunt. The response to vasodilator therapy (oxygen, prostacyclin, nitric oxide) may identify patients with hyperdynamic pulmonary hypertension. Selective pulmonary artery injections may be necessary if pulmonary venous obstruction is suspected because of high wedge pressure and low left ventricular end-diastolic pressure.

**TREATMENT**

The best management for patients who are at risk for the development of late pulmonary vascular disease is prevention by early surgical elimination of large intracardiac or great vessel communications during infancy. Some patients may be missed because they have not shown early clinical manifestations. Rarely, pulmonary vascular resistance never decreases at birth in these infants, and therefore they never acquire enough left-to-right shunting to become clinically apparent. Such delayed recognition is a particular risk in patients with congenital heart disease who live at high altitude. It is also a risk in infants with trisomy 21, who have a propensity for earlier development of pulmonary vascular disease. Because of the high incidence of congenital heart disease associated with trisomy 21, routine echocardiography is recommended at the time of initial diagnosis, even in the absence of other clinical findings.

Medical treatment of Eisenmenger syndrome is primarily symptomatic. Many patients benefit substantially from either oral (calcium channel blocker, endothelin antagonist, phosphodiesterase inhibitors) or chronic intravenous (prostacyclin) therapy. Combined heart-lung or bilateral lung transplantation is the only surgical option for many of these patients (see Chapter 443.2).

*Bibliography is available at Expert Consult.*
Bibliography


Most patients who have mild congenital heart disease require no treatment. The parents and child should be made aware that a normal life is expected and that no restriction of the child's activities is necessary. Overprotective parents may use the presence of a mild congenital heart lesion or even a functional heart murmur as a means to exert excessive control over their child's activities. Although fears may not be expressed overtly, the child may become anxious regarding early death or debilitation, especially when an adult member of the family acquires unrelated symptomatic heart disease. The family may have an unexpressed fear of sudden death, and the rarity of this manifestation should be emphasized in discussions directed at improving their understanding of the child's congenital heart defect. The difference between congenital heart disease and degenerative coronary disease in adults should be emphasized. General health maintenance, including a well-balanced, “heart-healthy” diet; aerobic exercise; and avoidance of smoking, should be encouraged.

Even patients with moderate to severe heart disease need not be restricted from all physical activity, although many will tend to limit their own activities. Physical education should be modified appropriately to the child's capacity to participate; the extent of such modification can often be guided by formal exercise testing. Although competitive sports for some patients may need to be discouraged, decisions are made on an individual basis. The influence of coach and peer pressure should be taken into account when recommending competitive versus noncompetitive athletics. Many cardiologists will also prohibit certain high-impact activities ("collision sports") such as tackle football or contact martial arts in patients with some forms of prior open heart surgery.

Routine immunizations should be given, with the inclusion of influenza vaccine during the appropriate season. Prophylaxis against the respiratory syncytial virus is recommended during respiratory syncytial virus season in young infants with unrepaired congenital heart disease and significant hemodynamic abnormalities. However, careful consideration for timing of administration of live-virus vaccination is required in patients who are potential candidates for heart or heart-lung transplantation.

Bacterial infections should be treated vigorously, but the presence of congenital heart disease is not an appropriate reason to use antibiotics indiscriminately. Prophylaxis against bacterial endocarditis should be carried out during dental procedures for appropriate patients. The American Heart Association has recently significantly revised these recommendations, with most patients no longer requiring routine prophylaxis (see Chapter 437). Endocarditis prophylaxis is generally no longer recommended for gastrointestinal or genitourinary procedures.

Cyanotic patients need to be monitored for noncardiac manifestations of oxygen deficiency (Table 434-1). Treatment of iron-deficiency anemia is important in cyanotic patients, who will show improved exercise tolerance and general well-being with adequate hemoglobin levels. These patients should also be carefully observed for excessive polycythemia. Cyanotic patients should avoid situations in which dehydration may occur, which leads to increased viscosity and increases the risk of stroke. Diuretics may need to be decreased or temporarily discontinued during episodes of acute gastroenteritis. High altitudes and sudden changes in the thermal environment should also be avoided. Phlebotomy with partial exchange transfusion is carried out only in symptomatic patients with severe polycythemia (usually those whose hematocrit is >65%).

Patients with moderate to severe forms of congenital heart disease or a history of rhythm disturbance should be carefully monitored during anesthesia for even routine surgical procedures. Consultation with an anesthesiologist experienced in the care of children with congenital heart disease is recommended. Women with nonrepaired severe congenital heart disease should be counseled on the risks associated with childbearing and on the use of contraceptives and tubal ligation. Pregnancy may be dangerous to both mother and fetus for patients with chronic cyanosis or pulmonary arterial hypertension. Women with mild to moderate heart disease and many of those who have had corrective surgery can have normal pregnancies, although those with residual hemodynamic derangements or with systemic right ventricles should be followed by a high-risk perinatologist and a cardiologist with expertise in caring for adults with congenital heart disease.

**POSTOPERATIVE MANAGEMENT**

After successful open heart surgery, the severity of the congenital heart defect, the age and condition (nutritional status) of the patient before surgery, the events in the operating room, and the quality of the postoperative care influence the patient’s course. Intraoperative factors that influence survival and that should be noted when a patient returns from the operating room include the duration of cardiopulmonary bypass, the duration of aortic cross-clamping (the time during which the heart is not being perfused), and the duration of profound hypothermia (used in some newborns: the period during which the entire body is not being perfused).

Immediate postoperative care should be provided in an intensive care unit staffed by a team of physicians, nurses, and technicians experienced with the unique problems encountered after open heart surgery in childhood. In most major centers, this occurs in a dedicated pediatric cardiovascular intensive care unit. Preparation for postoperative monitoring begins in the operating room, where the anesthesiologist...
Table 434-1 Extracardiac Complications of Cyanotic Congenital Heart Disease and Eisenmenger Physiology

<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>ETIOLOGY</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia</td>
<td>Persistent hypoxia</td>
<td>Phlebotomy</td>
</tr>
<tr>
<td>Relative anemia</td>
<td>Nutritional deficiency</td>
<td>Iron replacement</td>
</tr>
<tr>
<td>CNS abscess</td>
<td>Right-to-left shunting</td>
<td>Antibiotics, drainage</td>
</tr>
<tr>
<td>CNS thromboembolic stroke</td>
<td>Right-to-left shunting or polycythemia</td>
<td>Phlebotomy</td>
</tr>
<tr>
<td>Low-grade DIC, thrombocytopenia</td>
<td>Polycythemia</td>
<td>None for DIC unless bleeding, then phlebotomy</td>
</tr>
<tr>
<td>Hemoptyis</td>
<td>Pulmonary infarct, thrombosis, or rupture of pulmonary artery plexiform lesion</td>
<td>Embolization</td>
</tr>
<tr>
<td>Gum disease</td>
<td>Polycythemia, gingivitis, bleeding</td>
<td>Dental hygiene</td>
</tr>
<tr>
<td>Gout</td>
<td>Polycythemia, diuretic agent</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Arthritis, clubbing</td>
<td>Hypoxic arthropathy</td>
<td>None</td>
</tr>
<tr>
<td>Pregnancy complications: abortion, fetal growth retardation, prematurity increase, maternal illness</td>
<td>Poor placental perfusion, poor ability to increase cardiac output</td>
<td>Bed rest, pregnancy prevention counseling</td>
</tr>
<tr>
<td>Infections</td>
<td>Associated asplenia, DiGeorge syndrome, endocarditis</td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>Fatal RSV pneumonia with pulmonary hypertension</td>
<td>Ribavirin; RSV immunoglobulin (prevention)</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Increased oxygen consumption, decreased nutrient intake</td>
<td>Treat heart failure; correct defect early, increase caloric intake</td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
<td>S/P Fontan; high right-sided pressures</td>
<td>Oral budesonide or sildenafil</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>Injury to thoracic duct</td>
<td>Medium chain triglyceride diet Octreotide Surgical ligation of thoracic duct</td>
</tr>
<tr>
<td>Psychosocial adjustment</td>
<td>Limited activity, cyanotic appearance, chronic disease, multiple hospitalizations</td>
<td>Counseling</td>
</tr>
</tbody>
</table>

CNS, central nervous system; DIC, disseminated intravascular coagulation; RSV, respiratory syncytial virus; S/P, status post (after).

The electrocardiogram should be monitored continuously during the postoperative period. A change in heart rate, even without arrhythmia, may be the first indication of a serious complication such as hemorrhage, hypothermia, hyperventilation, or heart failure. **Cardiac rhythm disorders** must be diagnosed quickly because a prolonged untreated arrhythmia may add a severe hemodynamic burden to the heart in the critical early postoperative period (see Chapter 435). Injury to the heart's conduction system during surgery can result in postoperative complete heart block. This complication is usually temporary and is treated with surgically placed pacing wires that can later be removed. Occasionally, complete heart block is permanent. If heart block persists beyond 10–14 days postoperatively, insertion of a permanent pacemaker is required. Tachyarrhythmias are a common problem in postoperative patients. Junctional ectopic tachycardia can be a particularly troublesome rhythm to manage (see Chapter 435), although it usually responds to antiarrhythmic medications such as intravenous amiodarone.

**Heart failure** with poor cardiac output after cardiac surgery may be secondary to respiratory failure, serious arrhythmias, myocardial injury, blood loss, hypovolemia, a significant residual hemodynamic abnormality, or any combination of these factors. Treatment specific to the cause should be instituted. Catecholamines, phosphodiesterase inhibitors, nitroprusside and other afterload-reducing agents, and diuretics are the cardioactive agents most often used in patients with myocardial dysfunction in the early postoperative period (see Chapter 442). Postoperative pulmonary hypertension can be managed with hyperventilation and inhaled nitric oxide. In the rare patients who are unresponsive to standard pharmacologic treatment, various ventricular assist devices are available, depending on the patient’s size. If pulmonary function is adequate, a left ventricular assist device may be used. If pulmonary function is inadequate, extracorporeal membrane oxygenation may be used. These extraordinary measures are helpful in maintaining the circulation until cardiac function improves, usually

or surgeon places an arterial catheter to allow direct arterial pressure measurements and arterial sampling for blood gas determination. A central venous catheter is also placed for measuring central venous pressure and for infusions of cardiovascular medications. In more complex cases, right or left atrial or pulmonary artery catheters may be inserted directly into these cardiac structures and used for pressure monitoring purposes. Temporary pacing wires are placed on the atrium or ventricle, or both, in case temporary postoperative heart block occurs. Transcutaneous oximetry provides for continuous monitoring of arterial oxygen saturation. Near-infrared spectroscopy has been used to monitor cerebral and other end-organ perfusion in the perioperative period.

Functional failure of 1 organ system may cause profound physiologic and biochemical changes in another. Respiratory insufficiency, for example, leads to hypoxia, hypercapnia, and acidosis, which, in turn, compromise cardiac, vascular, and renal function. The latter problems cannot be managed successfully until adequate ventilation is reestablished. Thus, it is essential that the primary source of each postoperative problem be identified and treated.

**Respiratory failure** is a serious postoperative complication encountered after open heart surgery. Cardiopulmonary bypass carried out in the presence of pulmonary congestion results in decreased lung compliance, copious tracheal and bronchial secretions, atelectasis, and increased breathing effort. Because fatigue and, subsequently, hyperventilation and acidosis may rapidly ensue, mechanical positive pressure endotracheal ventilation is usually continued after open heart surgery for a minimum of several hours in relatively stable patients and for up to 2-3 days or longer in severely ill patients, especially infants. Patients with certain congenital heart lesions, particularly those with DiGeorge syndrome, may also have airway abnormalities (micrognathia, tracheomalacia, bronchomalacia) that can make both ventilation and extubation more difficult.
within 2-5 days. They have also been used as a bridge to transplantation in patients with severe nonremitting postoperative cardiac failure.

Acidosis secondary to low cardiac output, renal failure, or hypovolemia must be prevented, or if present, promptly corrected. Serial monitoring of arterial blood gases and lactate concentrations is performed. A low arterial pH may not only be a sign of decreased perfusion, but also worsen cardiac function and may be the forerunner of arrhythmias or cardiac arrest.

Renal function may be compromised by congestive heart failure and further impaired by prolonged cardiopulmonary bypass. Blood and fluid replacement, cardiac inotropic agents, and vaso dilators will usually reestablish normal urine flow in patients with hypovolemia or cardiac failure. Renal failure secondary to tubular injury may require temporary peritoneal or hemodialysis or hemofiltration.

Neurologic abnormalities can develop after cardiopulmonary bypass, especially in the neonatal period. Seizures may occur when the patient awakens from sedation and can usually be controlled with anticonvulsant medications. In the absence of other neurologic signs, self-limited isolated seizures in the immediate postoperative period usually carry a good long-term prognosis. Thromboembolism and stroke are rarer but serious complications of open heart surgery. In the long-term, both subtle and more substantial learning disabilities may develop. Patients who have undergone surgery entailing the use of cardiopulmonary bypass, especially in the newborn period, should be watched carefully during their early school years for signs of mild to moderate learning disabilities or attention deficit disorders, which are often amenable to early remedial intervention. The risk is higher in patients who have undergone repair using hypothermic total circulatory arrest than in those where systemic blood flow is maintained using cardiopulmonary bypass.

The postpericardiotomy syndrome may occur toward the end of the 1st postoperative wk or may sometimes be delayed until weeks or months after surgery. This febrile illness is characterized by fever, decreased appetite, listlessness, nausea, and vomiting. Chest pain is not always present, so a high index of suspicion should be maintained in any recently postoperative patient. Echocardiography is diagnostic. In most instances, the postpericardiotomy syndrome is self-limited; however, when pericardial fluid accumulates rapidly, the potential danger of cardiac tamponade should be recognized (see Chapter 440). Rarely, arrhythmias may also occur. Symptomatic patients usually respond to salicylates or indomethacin and bed rest. Occasionally, steroid therapy or pericardiotomy is required. Late recurrences are rare and can lead to chronic pericarditis.

Hemolysis of mechanical origin is seen, although rarely, after repair of certain cardiac defects, for example, atrioventricular septal defects (AVSDs), or after the insertion of a mechanical prosthetic valve. It is caused by unusual turbulence of blood at increased pressure. Reoperation may be necessary in rare patients with severe and progressive hemolysis who require frequent blood transfusions, but in most instances, the problem slowly regresses.

Infection is another potentially serious postoperative problem. Patients usually receive a broad-spectrum antibiotic for the initial postoperative period. Potential sites of infection include the lungs (generally related to postoperative atelectasis), the subcutaneous tissues at the incision site, the sternum, and the urinary tract (especially after an indwelling catheter has been in place). Sepsis with infective endocarditis is an infrequent complication, and can be difficult to manage, especially if prosthetic material was placed at the time of surgery (see Chapter 437).

**LONG-TERM MANAGEMENT**

Patients who have undergone surgery for congenital heart disease can be divided into several major categories: (1) lesions for which total repair has been achieved; (2) lesions for which both anatomic and physiologic correction have been achieved; and (3) lesions for which only palliation, albeit potentially long-term, has been achieved. There is some disagreement among cardiologists as to exactly which categories a particular congenital heart lesion might fall, and to some degree every case should be considered individually. Many argue that only for isolated patent ductus arteriosus is total repair really achieved, with no requirement for long-term follow-up. Patients who are able to undergo anatomic and physiologic correction include many of the left-to-right shunt lesions (atrial and ventricular septal defects) and milder forms of obstructive lesions (e.g., valvar pulmonic stenosis, some forms of valvar aortic stenosis, and coarctation of the aorta), and some forms of cyanotic heart disease, for example, uncomplicated tetralogy of Fallot and simple transposition of the great arteries. These patients usually have achieved total or near-total physiologic correction of their lesion; however, they are still at some risk of long-term sequelae, including late heart failure or arrhythmia, or recurrence of a significant physiologic abnormality (e.g., recoarctation of the aorta, worsening mitral regurgitation in patients with AVSDs, or long-standing pulmonary regurgitation in patients with tetralogy of Fallot repaired with a transannular patch). These patients require regular follow-up with a pediatric cardiologist (and when old enough, with an adult congenital heart disease specialist [see Chapter 434.1]); however, their long-term prognosis is generally very good, although some will require repeat surgeries. Patients with more complex lesions, such as those with single-ventricle physiology, are at much higher risk of long-term sequelae and require even closer follow-up. These patients, particularly those who have undergone the Fontan procedure, are at risk long-term for arrhythmia, thrombosis, protein losing enteropathy, end-organ (especially hepatic) dysfunction, and heart failure. Some may eventually require cardiac transplantation.

Physical limitations are variable, ranging from minimal to none in patients with physiologic correction, to mild to moderate in patients with palliative procedures. The extent to which a patient should be allowed to participate in athletics, both recreational and competitive, can best be determined by the cardiologist, often with the assistance of the data that can be derived from cardiopulmonary exercise testing (see Chapter 423.5).

Long-term morbidities affecting neurologic function and behavior are influenced by many factors, including the effects of any genetic alterations on the developing central nervous system. Data suggest a greater role for prenatal central nervous system abnormalities (anatomic or secondary to alterations in cerebral blood flow or oxygenation) than previously suspected; these include microcephaly, cerebral atrophy, and altered cerebral biochemistry. Chronic hypoxemia and failure to thrive also may influence the developing brain, and there is evidence that the type of intervention required (cardiopulmonary bypass, hypothermic total circulatory arrest, catheter-based therapy) plays a substantial role. In general, in the absence of a significant genetic syndrome or major perioperative complication, most children function at a fairly high level after repair of congenital heart defects and are able to attend regular school. Group mean scores on standard cognitive tests are not different from the general population; however, some areas appear to be more at risk than others, including certain aspects of motor function, speech, visual-motor tracking, and phonologic awareness. Awareness of these potential issues is critical to obtaining prompt remedial assistance if a child is found to be struggling in school.

**Bibliography is available at Expert Consult.**

### 434.1 Congenital Heart Disease in Adults

**Salil Ginde and Michael G. Earing**

The advent of cardiac surgical procedures such as ligation of patent ductus arteriosus, resection of coarctation of aorta, and the Blalock-Taussig shunt, as well as advances in diagnostic, interventional, and critical care skills have resulted in survival of approximately 90% of children with congenital heart disease to adulthood. More adults than children are living with congenital heart disease in the United States, with a 5% increase every year. In the last decade, 35% of hospitalizations for congenital heart disease were patients over the age of 18 yr (mean age: 55 yr).

**LONG-TERM MEDICAL CONSIDERATIONS**

Approximately 25% of adults with congenital heart disease have a mild form that has allowed them to survive into adulthood without surgical...
Bibliography


or interventional cardiac catheterization. The most common lesions in this category include mild aortic valve stenosis (usually in setting of bicuspid aortic valve), small restrictive ventricular septal defects, mild pulmonary valve stenosis, and mitral valve prolapse (Table 434-2). These patients need less-frequent follow-up to assess for progression of disease and to identify associated complications. The majority of adults with congenital heart disease living in the United States are patients who have had previous intervention (Table 434-3). Although most children who undergo surgical intervention will survive to adulthood, with few exceptions, total correction is not the rule. The few exceptions include patent ductus arteriosus, ventricular septal defects, and atrial septal defects; this is true only if they are closed early before the development of irreversible pulmonary vascular changes, and no residual lesions exist.

Because adult patients with congenital heart disease (CHD) are surviving longer than ever, it is becoming increasingly apparent that even the simplest lesions can be associated with long-term complications. These long-term complications include both cardiac and noncardiac problems (Tables 434-4 and 434-5, Fig. 434-1). Cardiac complications include arrhythmias and conduction defects, ventricular dysfunction, residual shunts, valvular lesions (regurgitation and stenosis), hypertension, and aneurysms. Noncardiac sequelae (comorbidities) include pulmonary, renal, and hepatic dysfunction that is caused either directly or indirectly by the underlying CHD. Abnormal pulmonary function most commonly presents as restrictive lung physiology, and likely results from prior sternotomy or thoracotomy, scoliosis, diaphragmatic dysfunction, or parenchymal lung disease. Reduced pulmonary function contributes to reduced exercise tolerance and is a risk factor for mortality in adults with CHD. Renal dysfunction may result from chronic cyanosis, multiple surgeries requiring cardiopulmonary bypass, or from other comorbid conditions, such as hypertension and diabetes mellitus. Hepatic injury from chronic liver congestion in patients with elevated central venous pressures, particularly patients palliated with the Fontan procedure, can result in hepatic fibrosis, cirrhosis, hepatic dysfunction and rarely hepatocellular carcinoma. Adults with CHD are at risk for developmental abnormalities such as intellectual impairment, somatic abnormalities such as facial dysmorphism (cleft palate/lip), central nervous abnormalities such as seizure disorders from previous thromboembolic events or cerebrovascular accidents, and impairments of hearing or vision loss. Psychosocial problems involving employment, life and health insurance, participation in sports, sexual activity, and contraception are common. As a result of these long-term complications, the majority of adults with CHD need lifelong follow-up. When adults with CHD are hospitalized, it is usually for heart failure or an arrhythmia; others may require catheterization or another cardiac surgical procedure.

### SPECIFIC LESIONS

#### Left-to-Right Shunts

If the initial lesion has a shunt that is large and nonrestrictive (allowing transmission of near systemic pressure to the pulmonary arteries), irreversible pulmonary vascular changes can occur, resulting in pulmonary hypertension at systemic levels with reversed or bidirectional shunting at the level of the defect (Eisenmenger syndrome) (see Chapter 433.2).

#### Atrial Septal Defects

See Chapter 426.1.

Although, most individuals with an atrial septal defect are diagnosed during childhood after a murmur is noted, a minority of patients

**Table 434-2**

<table>
<thead>
<tr>
<th>Congenital Heart Defects Associated with Survival into Adulthood Without Surgery or Interventional Cardiac Catheterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pulmonary valve stenosis</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
</tr>
<tr>
<td>Small to moderate size atrial septal defect</td>
</tr>
<tr>
<td>Small ventricular septal defect</td>
</tr>
<tr>
<td>Small patent ductus arteriosus</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Partial atroventricular canal (ostium primum atrial septal defect and cleft mitral valve)</td>
</tr>
<tr>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>Ebstein anomaly</td>
</tr>
<tr>
<td>Congenitally corrected transposition (atrioventricular and ventriculoarterial discordance)</td>
</tr>
</tbody>
</table>

**Table 434-3**

<table>
<thead>
<tr>
<th>Most Common Congenital Heart Defects Surviving to Adulthood After Surgery or Interventional Catheterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve disease following balloon valvuloplasty or surgical valvotomy</td>
</tr>
<tr>
<td>Pulmonary valve stenosis following balloon valvuloplasty or surgical valvotomy</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td>Complete atroventricular canal defect</td>
</tr>
<tr>
<td>Transposition of the great arteries</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>Complex single ventricles after the modified Fontan procedure</td>
</tr>
</tbody>
</table>

**Table 434-4**

<table>
<thead>
<tr>
<th>Risks in Adults Who Have Congenital Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm disorder</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>Heart block</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td>Acquired lesions</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>Sudden death</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
</tr>
<tr>
<td>Essential hypertension</td>
</tr>
<tr>
<td>Recoarctation</td>
</tr>
<tr>
<td>Aneurysm formation</td>
</tr>
<tr>
<td>Pregnancy risk (see Table 434-5)</td>
</tr>
<tr>
<td>Residual lesions (shunts)</td>
</tr>
</tbody>
</table>

**Table 434-5**

<table>
<thead>
<tr>
<th>Lesion Specific Risks of Maternal and Neonatal Complications of Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No additional risk</td>
</tr>
<tr>
<td>Small septal defects</td>
</tr>
<tr>
<td>Surgically closed ASD, VSD, PDA</td>
</tr>
<tr>
<td>Mild to moderate aortic regurgitation</td>
</tr>
<tr>
<td>Mild to moderate pulmonary stenosis</td>
</tr>
<tr>
<td>Slightly increased risk</td>
</tr>
<tr>
<td>Postoperative repair of tetralogy of Fallot</td>
</tr>
<tr>
<td>Transposition of the great arteries, s/p arteriovenous fistula</td>
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<tr>
<td>Transposition of the great arteries, s/p arteriovenous fistula, surgical repair</td>
</tr>
<tr>
<td>Moderate risk</td>
</tr>
<tr>
<td>Transposition of the great arteries, s/p atrial switch procedure</td>
</tr>
<tr>
<td>Congenitally corrected transposition of the great arteries</td>
</tr>
<tr>
<td>Single ventricle physiology, s/p Fontan procedure</td>
</tr>
<tr>
<td>Severe risk</td>
</tr>
<tr>
<td>Cyanotic congenital heart disease, unoperated or palliated</td>
</tr>
<tr>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>Prosthetic valves</td>
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<tr>
<td>Obstructive lesions including coarctation</td>
</tr>
<tr>
<td>Pregnancy contraindicated</td>
</tr>
<tr>
<td>Severe pulmonary hypertension</td>
</tr>
<tr>
<td>Severe obstructive lesions</td>
</tr>
<tr>
<td>Marfan syndrome, aortic root &gt;40 mm</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; PDA, patent ductus arteriosus; s/p, status post (after); VSD, ventricular septal defect.
Important issues that are crucial to address at time of transition. (From Spence MS, Balaratnam MS, Gatzoulis MA: Clinical update: cyanotic adult congenital heart disease, Lancet 370:1530–1532, 2007, p. 1531.)

Present with symptoms for the 1st time as adults. Most patients are asymptomatic during the 1st and 2nd decades of life. In the 3rd decade, an increasing number of patients then develop exercise intolerance, palpitations from atrial arrhythmias, and cardiac enlargement. If untreated, survival into adulthood is the rule; life expectancy, however, is not normal and there is significant long-term morbidity. After the age of 40 yr, the mortality rate increases by 6% per year, and more than 20% of patients will have developed atrial fibrillation. By age 60 yr, the number of patients with atrial fibrillation increases to more than 60%.

Late Outcome Following Closure of Atrial Septal Defect
Most patients who have undergone early closure of a defect will have excellent long-term survival with low morbidity if repair is undertaken before age 25 yr. Older age of repair is associated with decreased late survival with an associated increased risk for the development of atrial arrhythmias, thromboembolic event, and pulmonary hypertension. Long-term complications and survival following transcatheter device closure remain unknown; early and intermediate results are excellent with a high rate of atrial septal defect closure and few major complications.

Ventricular Septal Defects
See Chapter 426.6.

Although isolated ventricular septal defects (VSDs) are 1 of the most common forms of CHD, the diagnosis of a VSD in an adult is rare. The primary reason for this is that most patients with a hemodynamically significant VSD will have undergone repair in childhood or will have died earlier in life. As result, the spectrum of isolated VSD in adults is limited to (1) those with small restrictive defects, (2) those with Eisenmenger syndrome, and (3) those who had their defects closed in childhood.

For patients with small restrictive VSD, the long-term survival is excellent with estimated 25-yr survival of 96%. In addition, the long-term morbidity for patients with a restrictive VSD also appears to be low. Their clinical course is not completely benign. Reported long-term complications include endocarditis, progressive aortic regurgitation secondary to prolapse of aortic valve into the defect (highest risk is with suprasicrimal type, but also can occur in setting of perimembranous defect), and the development of both right and left outflow tract obstruction from a double-chamber right ventricle or a subaortic membrane. For those patients who develop Eisenmenger syndrome, survival into the 3rd decade is common. With increasing age, the long-term complications of right-heart failure, paradoxical emboli, and polycythemia, usually result in progressive decline in survival, with an average age of death of 37 yr.

Adults with previous VSD closure, without pulmonary hypertension or residual defects, live a normal life expectancy. Because patients with small VSDs are asymptomatic, these patients should be managed conservatively. Given the long-term risks, they do need intermittent follow-up for life to monitor for the development of late complications. The exception to this rule is patients with small suprasicrimal or perimembranous VSD with associated prolapse of the aortic cusp into the defect resulting in progressive aortic regurgitation. These patients should be considered for surgical repair at the time of diagnosis to prevent progressive aortic valve damage.

Complete Atrioventricular Canal
See Chapter 426.5.

The natural history for patients with complete AVSD is characterized by the early development of pulmonary vascular disease, leading to irreversible damage often by age 1 yr (especially in children with Down syndrome). Thus, patients who present in adulthood can be categorized into 2 groups: (1) those with Eisenmenger syndrome and (2) those who had their defects closed in childhood.

Overall, for those patients who underwent early repair before the development of pulmonary vascular disease, the long-term prognosis is good. The most common long-term complication is left atrioventricular valve regurgitation, with approximately 5-10% of patients requiring surgical revision for left atrioventricular valve repair or replacement during follow-up. The second most common long-term complication for this patient group is subaortic stenosis, occurring in up to 5% of patients after repair. Other long-term complications include residual atrial or ventricular level shunts, complete heart block, atrial and ventricular arrhythmias, and endocarditis.

For those patients who have developed Eisenmenger syndrome, all are symptomatic with exertional dyspnea, fatigue, palpitations, edema, and syncope. Survival is similar to other forms of Eisenmenger syndrome, with a mean age of death of 37 yr. Strong predictors for death include syncope, age at presentation of symptoms, poor functional class, low oxygen saturation (<85%), elevated serum creatinine and serum uric acid concentrations, and Down syndrome.

Patients who underwent previous repair and develop significant left atrioventricular valve regurgitation causing symptoms, atrial arrhythmias, or deterioration in ventricular function should undergo elective valve repair or replacement. Those previously repaired patients who develop significant subaortic stenosis (defined as a peak cardiac catheterization or echo gradient of >50 mm Hg) should undergo surgical repair.

Patent Ductus Arteriosus
See Chapter 426.8.

A patent ductus arteriosus (PDA) is usually an isolated lesion in the adult patient. The size of the defect is the primary determinant of clinical course in the adult patient. These clinical courses can be grouped
into 5 main categories: (1) silent PDAs; (2) small, hemodynamically insignificant PDAs; (3) moderate size PDAs; (4) large PDAs; and (5) previously repaired PDAs.

A silent PDA is a tiny defect that cannot be heard by auscultation and is only detected by other nonclinical means such as echocardiography. Life expectancy is always normal in this population and the risk for endocarditis is extremely low.

Patients with a small PDA have an audible long-ejection or continuous murmur heard best at the left upper sternal border that radiates to the back. In addition, they have normal peripheral pulses. Because there is negligible left to right shunting these patients have normal left aorta and left ventricle (LV) size and normal pulmonary artery pressure by echocardiography and chest x-ray. These patients like those with silent PDAs are asymptomatic and live a normal life expectancy. They have a higher risk for endocarditis.

Patients with moderate size PDAs may present during adulthood. These patients often will have wide, bounding peripheral pulses and an audible continuous murmur. These patients all have significant volume overload and develop some degree of left aorta and LV enlargement and some degree of pulmonary hypertension. These patients are symptomatic with dyspnea, palpitations, syncope, and sudden death.

Patients with large PDAs typically present with signs of severe pulmonary hypertension and Eisenmenger syndrome. By adulthood, the continuous murmur is typically absent and there is differential cyanosis (lower extremity saturations lower than the right arm saturation). These patients have a similar prognosis as other patients with Eisenmenger syndrome.

Patients who underwent repair of a PDA prior to the development of pulmonary hypertension have a normal life expectancy without restrictions. All patients with clinical evidence of a PDA are at increased risk for endocarditis. As result, all PDAs except for small silent PDAs and those patients with severe irreversible pulmonary hypertension should be considered for closure. Catheter device closure is the preferred method in most centers today. Surgical closure is reserved for patients with PDAs too large for device closure or when the anatomy is distorted, such as in the setting of a large ductal aneurysm.

Cyanotic Heart Disease
See Chapters 429, 430, and 431.

Unlike the acyanotic forms of CHD, the majority of patients with cyanotic CHD will have had at least 1 and often several previous interventions prior to adulthood. The most frequent defects seen in the outpatient adult congenital setting is tetralogy of Fallot, complete transposition of the great arteries (TGA, also known as d-transposition), pulmonary valve stenosis, and various forms of single ventricles. Other defects include total anomalous pulmonary venous return, truncus arteriosus, and double-outlet right ventricle.

Tetralogy of Fallot
See Chapter 430.1.

In the developed world, the unoperated adult patient with tetralogy of Fallot has become a rarity because the majority of patients will have undergone palliation or, more often, repair in childhood. Survival in the unoperated patient to the 7th decade has been described but is rare. In general, only 11% of unoperated patients are alive by age 20 yr and only 3% by age 40 yr.

Late survival following repair of tetralogy of Fallot is excellent. Repair is typically performed at 3-12 mo of age and consists of patch closure of the VSD and relief of the pulmonary outflow tract obstruction by patch augmentation of the right ventricular outflow tract, pulmonary valve annulus, or both. Survival rates at 32 and 25 yr have been reported to be 86% and 85%, respectively, compared to 95% in age- and sex-matched controls. Most patients lived an unrestricted life. Many patients do develop late symptoms that include exertional dyspnea, palpitations, syncope, and sudden cardiac death. Late complications include endocarditis, aortic regurgitation with or without aortic root dilation (typically caused by damage of the aortic valve during VSD closure or secondary to an intrinsic aortic root abnormality), LV dysfunction (secondary to inadequate myocardial protection during previous repair or chronic left ventricular volume overload caused by long-standing palliative arterial shunts), residual pulmonary valve obstruction, residual pulmonary valve regurgitation, right ventricular (RV) dysfunction (as a result of pulmonary regurgitation or pulmonary stenosis), atrial arrhythmias (typically atrial flutter), ventricular arrhythmias, and heart block.

Reintervention is necessary in approximately 10% of patients following reparative surgery at 20-year follow-up. With longer follow-up, the incidence of reintervention continues to increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary valve regurgitation.

Transposition of the Great Arteries
See Chapter 431.1.

The natural history of patients with un repaired TGA is so poor that very few patients survive past childhood without intervention. The first definitive operations for TGA were described by Dr. Senning in 1959 and Dr. Mustard in 1964 (atrial switch procedures). With these procedures, the systemic and pulmonary venous returns are rerouted in the atrium by constructing baffles. The systemic venous return from the superior and inferior vena cavae is directed through the mitral valve and into the LV (connected to the pulmonary artery). The pulmonary venous return is then directed through the tricuspid valve into the right ventricular (connected to the aorta). These procedures can be performed with low mortality but leave the LV as the pulmonary ventricle and the right ventricle as the systemic ventricle. Long-term follow-up studies after the atrial switch procedure show a small but ongoing attrition rate with numerous other intermediate and long-term complications. Two specific problems after the atrial switch procedure are most concerning. These include the loss of sinus rhythm with the development of atrial arrhythmias, occurring at an incidence of 50% by age 25 yr, and the development of systemic ventricular dysfunction, occurring at an incidence of 50% by age 35 yr. Other long-term complications include endocarditis, baffle leaks, baffle obstruction, tricuspid valve regurgitation, and sinus node dysfunction requiring pacemaker placement.

As result of these long-term complications, the arterial switch operation has become the procedure of choice to treat these patients since 1985. During the arterial switch procedure, the great arteries are transected and reanastomosed to the correct ventricle (LV to the aorta and the right ventricle to the pulmonary artery) with coronary artery transfer. Operative survival after the arterial switch procedure in the current surgical era is very good, with a surgical mortality rate of 2-5%. Long-term data on survival and complications does not exist, but intermediate results are promising. Reported intermediate complications include endocarditis, pulmonary outflow tract obstruction (at the supravalvular level or at the takeoff of the peripheral pulmonary arteries), aortic valve regurgitation, and coronary artery compromise (ranging from minor stenosis to complete occlusion).

Because of the high incidence of observed and potential medical problems, all patients who have had both atrial and arterial repair of TGA should have lifelong follow-up by a cardiologist at a center specializing in adult CHD.

Pulmonary Valve Stenosis
See Chapter 427.1.

Most patients with pulmonary valve stenosis are asymptomatic and present with a cardiac murmur. Survival into adult life and the need for intervention however is directly correlated to the degree of obstruction. Patients with trivial stenosis (defined as a peak gradient <25 mm Hg) followed for 25 yr remain asymptomatic and have no significant progression of obstruction over time. For those patients with moderate pulmonary valve stenosis (defined as a peak gradient of 25-49 mm Hg), there is an approximately 20% chance of requiring intervention by age 25 yr. For those patients with severe stenosis (defined as a peak gradient of >50 mm Hg), the majority ultimately require an intervention, either surgery or balloon valvuloplasty by age 25 yr.
Following surgical valvotomy for isolated pulmonary stenosis, long-term survival is excellent. With longer follow-up the incidence of late complications and the need for reintervention do increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary regurgitation. Other long-term complications include recurrent atrial arrhythmias, endocarditis, and residual RV outflow tract obstruction.

Patients with moderate to severe pulmonary stenosis (defined as a peak gradient of >50 mm Hg) should be considered for intervention even in the absence of symptoms. Since 1985, percutaneous balloon valvuloplasty has been the accepted treatment for patients of all ages. Prior to 1985, surgical valvotomy had been the gold standard. Surgical valvotomy is reserved for those patients who are unlikely to have successful results from balloon valvuloplasty, such as those with an extremely dysplastic or calcified valve.

Left-Sided Obstructive Lesions
Coarctation of the Aorta

See Chapter 427.6.

The clinical presentation of coarctation of the aorta depends on the severity of obstruction and the associated anomalies. Unrepaired coarctation of the aorta typically presents with symptoms prior to adulthood. These symptoms include headaches related to hypertension, leg fatigue or cramps, exercise intolerance, and systemic hypertension. Those untreated patients surviving to adulthood thus typically have only mild coarctation of the aorta. In the era prior to surgery, without treatment the mean age of death was 32 yr. Causes of death included left ventricular failure, intracranial hemorrhage, endocarditis, aortic rupture/dissection, and premature coronary artery disease.

Following surgical repair, long-term survival is good but is directly correlated with the age at repair, with those repaired after age 14 yr having a lower 20 yr survival than those who were repaired earlier, 91% compared to 79%. With longer follow-up the incidence of long-term complications continues to rise. The most common long-term complication is persistent or new systemic hypertension at rest or during exercise. Other long-term complications include aneurysms of the ascending or descending aorta, recoarctation at the site of previous repair, coronary artery disease, aortic stenosis or regurgitation (in setting of bicuspid aortic valve), rupture of an intracranial aneurysm, and endocarditis.

Patients with significant native or residual coarctation of the aorta (symptomatic patients with a peak gradient across the coarctation of >20 mm Hg) should be considered for intervention, either surgery or catheter intervention with balloon angioplasty with or without stent placement. Surgical repair in the adult patient is technically difficult and is associated with high morbidity. Catheter based intervention has become the preferred method in most experienced adult CHD centers.

Aortic Valve Stenosis

See Chapter 427.5.

The natural history of aortic valve stenosis in adults is quite variable but is characterized by progressive stenosis over time. By age 45 yr, approximately 50% of bicuspid aortic valves will have some degree of stenosis.

Most patients with aortic valve stenosis are asymptomatic and are diagnosed after a murmur is detected. The severity of obstruction at the time of diagnosis correlates with the pattern of progression. Symptoms are rare until patients have severe aortic valve stenosis (mean gradient by echocardiography of >40 mm Hg). Symptoms include chest pain, exertional dyspnea, near syncope, and syncope. When any of these symptoms are present, the risk of sudden cardiac death is very high and as result, surgical intervention is mandated. For patients requiring surgical valvotomy to relieve the stenosis prior to adulthood, the majority of patients do well. However, at 25 yr follow-up, up to 40% of patients will have required a second operation for residual stenosis or regurgitation.

Patients with symptoms and severe aortic valve stenosis should be considered for intervention. Treatment involves manipulating the valve to reduce stenosis. This can be accomplished by transvenous balloon dilation of the valve, open surgical valvotomy, or valve replacement. In absence of significant aortic regurgitation, most centers favor balloon dilation or surgical valvotomy for children and young adults who have pliable valves with fusion of commissures. In older adults, aortic valve replacement is the treatment of choice.

Endocarditis Prophylaxis

See Chapter 437.

The American Heart Association found that very few cases of endocarditis are prevented with antibiotic prophylaxis. Only patients with cardiac conditions associated with the highest risk for adverse outcomes should continue follow antibiotic prophylaxis before surgery: patients with previous endocarditis, unrepaired cyanotic CHD, including palliative shunts and conduits; completely repaired congenital heart defects with prosthetic material or device, whether placed by surgery or by catheter intervention, during the 1st 6 mo after the procedure; and repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization). Except for the conditions just listed, antibiotic prophylaxis is no longer recommended for other forms of CHD.

PREGNANCY AND CONGENITAL HEART DISEASE

CHD is the most common form of heart disease encountered during pregnancy in developed countries. Heart disease does not preclude a successful pregnancy but increases the risk to both the mother and the baby. During pregnancy there are substantial hemodynamic changes that occur. The hemodynamic changes in pregnancy result in a steady increase in cardiac output during pregnancy until the 32nd wk of gestation, at which time, the cardiac output reaches a plateau at 30-50% above the prepregnancy level. At time of delivery, with uterine contractions an additional 300-500 mL of blood enters the circulation. This in conjunction with increased blood pressure and heart rate during labor increases the cardiac output at delivery to 80% the prepregnancy level.

Despite these hemodynamic changes, the outcome of pregnancy is favorable in most women with CHD provided that functional class and systemic ventricular function are good (see Table 434-5). Pulmonary artery hypertension presents a serious risk during pregnancy, particularly when the pulmonary pressure exceeds 70% of systemic pressure, regardless of functional class. Other contraindications to pregnancy include severe obstructive left-sided lesions (coarctation of the aorta, aortic valve stenosis, mitral valve stenosis, hypertrophic cardiomyopathy), Marfan syndrome with coexisting dilated ascending aorta (defined as >4 cm), persistent cyanosis, and systemic ventricular dysfunction (ejection fraction of ≤40%). The need for full anticoagulation during pregnancy, although not a contraindication, poses an increased risk to both mother and fetus. The relative risks and benefits of the different anticoagulant approaches need to be discussed fully with the prospective mother.

Pregnancy counseling should begin early in adolescence and should be part of the routine cardiac follow-up visit. During counseling, a discussion about the risk of CHD in the offspring should take place. In the general population, the incidence of CHD is 1%. In the offspring of a mother with CHD, the risk increases to 5-6%. Often the cardiac lesion in the offspring is not the same as that in the mother, except for in the case of a syndrome with autosomal dominant inheritance (Marfan syndrome, hypertrophic cardiomyopathy). Risk stratification should include the specific CHD lesion but also needs to take in account the maternal functional class. Although the specific CHD lesion is important, multiple studies demonstrate that the maternal functional class prior to pregnancy is highly predictive of both maternal and fetal outcomes, with those having the best functional class having the best outcomes.

CONTRACEPTION

A critical part of caring for adults with CHD is to provide or make available advice on contraception. Unfortunately, there are limited data on the safety of various contraceptive techniques in adult CHD patients. The estrogen-containing oral contraceptive pill can be used in many adult CHD patients but is not recommended in adult CHD patients at risk of thromboembolism, such as those with cyanosis, prior
Fontan procedure, atrial fibrillation, or pulmonary artery hypertension. In addition, this form of contraceptive therapy may upset anticoagulation control. Although slightly less effective than contraceptive pills containing combined estrogen/progesterone, medroxyprogesterone, the progesterone-only pills, and levonorgestrel are good options for most adult CHD patients. Medroxyprogesterone and levonorgestrel, however, can cause fluid retention and thus need to be used with caution in patients with heart failure. These medications are also associated with depression and often breakthrough bleeding. Tubal ligation, although the most secure method of contraception, can be a high-risk procedure in patients with complex CHD or those with pulmonary hypertension. Hysteroscopic sterilization (Essure) may be reasonable for high-risk patients. In the past, intrauterine devices were seldom used in cardiac patients because of the associated risk of bacteremia, pelvic inflammatory disease, and endocarditis. Intrauterine devices such as the Mirena, appear to be safe and effective, and are rapidly becoming one of the most commonly used form of contraception in the adult CHD population.

**ADOLESCENT TRANSITION**

It is well recognized that, as part of the process of obtaining independence, adolescents or young adults must develop a forward-looking, independent approach to their medical care. For children with heart disease, the transition process must begin during early adolescence and should be encouraged by both the primary care provider and the pediatric cardiologist, who must identify an appropriate adult congenital heart program to which transition and transfer will be made at an appropriate time (Table 434-6).

A successful transition program includes the following elements:

- Development of a written transition plan that should begin by the age of 14 yr
- Because adolescents and young adults are frequently unaware of the details of their cardiac diagnosis and history, a complete, concise, portable medical record, including all pertinent aspects of cardiac care, should be shared with adolescents and their families and prepared for transmittal to the eventual adult care destination.
- The primary care provider and cardiologist must address unique adolescent medical issues as they impact the cardiovascular system. In addition to medical problems, education, vocational planning, psychosocial issues, and access to medical care are all topics that should be discussed with adolescents and their families.

There is a tendency for young adults to avoid medical care because of lack of education, denial, or difficulty with access to the medical care system. Thus, a critical goal of the adolescent transition process is to identify an appropriate site for ongoing medical care and ensure maintenance of the medical record and continuity of care for the young adult. The site of care for a young adult with CHD may be a pediatric program or facility, or may be a specialized center or program for the adult with CHD. The critical issues are the continuity of care, the preparation of the patient, and the patient's participation in the process.

*Table 434-6*  
**Issues That Require Coordination of Care Between the Cardiologist and the Primary Care Physician**

<table>
<thead>
<tr>
<th>Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic prophylaxis for endocarditis</td>
</tr>
<tr>
<td>Medications and drug interactions</td>
</tr>
<tr>
<td>Anticoagulation with prosthetic valves</td>
</tr>
<tr>
<td>Exercise and sports participation</td>
</tr>
<tr>
<td>Educational and vocational planning</td>
</tr>
<tr>
<td>Contraception and pregnancy</td>
</tr>
<tr>
<td>Drug, alcohol, and tobacco use</td>
</tr>
<tr>
<td>Noncardiac surgical planning</td>
</tr>
<tr>
<td>Anesthetic issues</td>
</tr>
<tr>
<td>New symptoms or acute illnesses</td>
</tr>
<tr>
<td>Coexistent medical conditions</td>
</tr>
<tr>
<td>Travel</td>
</tr>
</tbody>
</table>

*Bibliography is available at Expert Consult.*
Bibliography


The term *arrhythmia* refers to a disturbance in heart rate or rhythm. Such disturbances can lead to heart rates that are abnormally fast, slow, or irregular. They may be transient or incessant, congenital or acquired, or caused by a toxin or by drugs. They may be associated with particular forms of congenital heart disease, may be a complication of surgical repair of congenital heart disease, may be a result of certain genetic causes, or may be a result of fetal inflammation such as in maternal connective tissue disease. Arrhythmias, either slow or fast, may lead to acutely decreased cardiac output, degeneration into a more dangerous arrhythmia such as ventricular fibrillation, or if incessant may lead to cardiomyopathy. Arrhythmias may lead to syncope or to sudden death. When a patient has an arrhythmia, it is important to determine whether the particular rhythm is likely to lead to severe symptoms or to deteriorate into a life-threatening condition. Rhythm abnormalities, such as single premature atrial and ventricular beats, are common and in children without heart disease, in most instances do not pose a risk to the patient.

A number of pharmacologic agents are available for treating arrhythmias; many have not been studied extensively in children. Insufficient data are available regarding pharmacokinetics, pharmacodynamics, and efficacy in the pediatric population, and therefore the selection of an appropriate agent is necessarily empirical. Fortunately, the majority of rhythm disturbances in children can be reliably controlled with a single agent (Table 435-1). Increasingly, transcatheter ablation is acceptable therapy not only for life-threatening or drug-resistant arrhythmias, but also for the cure of arrhythmias. For patients with bradycardia, implantable pacemakers are small enough for use in all ages, and even in premature infants. Implantable cardioverter-defibrillators (ICDs) are available for use in high-risk patients with malignant ventricular arrhythmias and an increased risk of sudden death.

### 435.1 Principles of Antiarrhythmic Therapy

When considering drug therapy in the pediatric population, it is important to recognize that there may be marked differences in pharmacokinetics by age and in comparison with adults. Infants may have slower absorption, slow gastric emptying, and differing sizes of drug tissue compartments affecting the volume of distribution. Hepatic metabolism and renal excretion may vary within the pediatric age group as well as in comparison to adults. When considering antiarrhythmic therapy, it is important to recognize that the likely arrhythmia mechanism may be different for the pediatric vs. adult population.

There are many antiarrhythmic agents available for rhythm control. The majority have not been approved by the FDA for use in children; their use is therefore considered “off-label.” Pediatric cardiologists have experience with these drugs, and there are well-recognized standards regarding dosing.
With the availability of potentially curative ablation procedures, medical therapy has become less important. Clinicians and patients accept fewer drug side effects. Intolerable side effects, as well as the potential for a proarrhythmia induced by an antiarrhythmic drug, can seriously limit medical therapy and will lead the physician and family toward a potentially curative ablation procedure.

Antiarrhythmic drugs are commonly categorized using the Vaughan Williams classification system. This system comprises 4 classes: Class I includes agents that primarily block the sodium channel, class II includes the β-blockers, class III includes those agents that prolong repolarization, and class IV are the calcium channel blockers. Class I is further divided by the strength of the sodium channel blockade (see Table 435-1).

### Table 435-1: Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class

<table>
<thead>
<tr>
<th>CLASS IA: INHIBITS NA+ FAST CHANNEL, PROLONGS REPOLARIZATION</th>
<th>DRUG</th>
<th>INDICATIONS</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
<th>INTERACTIONS</th>
<th>DRUG LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>SVT, atrial fibrillation, atrial flutter, VT</td>
<td>Oral: 30-60 mg/kg/24 hr divided q6h</td>
<td>Nausea, vomiting, diarrhea, fever, cinchonism, QRS and QT prolongation, AV nodal block, asystole syncope, thrombocytopenia, hemolytic anemia, SLE, blurred vision, convulsions, allergic reactions, exacerbation of periodic paralysis</td>
<td>Enhances digoxin, may increase PTT when given with warfarin</td>
<td>2-6 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td>SVT, atrial fibrillation, atrial flutter, VT</td>
<td>Oral: 15-50 mg/kg/24 hr divided q6h Max dose: 4 g/24 hr IV: 10-15 mg/kg over 30-45 min load followed by 20-80 µg/kg/min Max dose: 2 g/24 hr</td>
<td>PR, QRS, QT interval prolongation, anorexia, nausea, vomiting, rash, fever, agranulocytosis, thrombocytopenia, Coombs-positive hemolytic anemia, SLE, hypotension, exacerbation of periodic paralysis Anticholinergic effects, urinary retention, blurred vision, dry mouth, QT and QRS prolongation, hepatic toxicity, negative inotropic effects, agranulocytosis, psychosis, hypoglycemia, proarrhythmia</td>
<td>Toxicity increased by amiodarone and cimetidine</td>
<td>4-8 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>SVT, atrial fibrillation, atrial flutter</td>
<td>Oral: &lt;2 yr: 20-30 mg/ kg/24 hr divided q6h or q12h (long-acting form); 2-10 yr: 9-24 mg/kg/24 hr divide q6h or q12h (long-acting form); 11 yr: 5-13 mg/kg/24 hr divided q6h or q12h (long-acting) Max dose: 1.2 g/24 hr</td>
<td></td>
<td></td>
<td>2-5 µg/ml</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS IB: INHIBITS NA+ FAST CHANNEL, SHORTENS REPOLARIZATION</th>
<th>DRUG</th>
<th>INDICATIONS</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
<th>INTERACTIONS</th>
<th>DRUG LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>VT, VF</td>
<td>IV: 1 mg/kg repeat q 5 min 2 times followed by 20-50 µg/kg/min (max dose: 3 mg/kg)</td>
<td>CNS effects, confusion, convulsions, high grade AV block, asystole, coma, paresthesias, respiratory failure Gl upset, skin rash, neurologic Rash, gingival hyperplasia, ataxia, lethargy, vertigo, tremor, macrocytic anemia, bradycardia with rapid push</td>
<td>Propranolol, cimetidine, increases toxicity</td>
<td>1-5 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>VT</td>
<td>Oral: 6-15 mg/kg/24 hr divided q6h</td>
<td></td>
<td>Cimetidine</td>
<td>0.8-2 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Digitalis intoxication</td>
<td>Oral: 3-6 mg/kg/24 hr divided q12h Max dose: 600 mg IV: 10-15 mg/kg over 1 hr load</td>
<td></td>
<td>Amiodarone, oral anticoagulants, cimetidine, nifedipine, disopyramide, increase toxicity</td>
<td>10-20 µg/mL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLASS IC: INHIBITS NA+ CHANNEL</th>
<th>DRUG</th>
<th>INDICATIONS</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
<th>INTERACTIONS</th>
<th>DRUG LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>SVT, atrial tachycardia, VT</td>
<td>Oral: 6.7-9.5 mg/kg/24 hr divided q6h In older children, 50-200 mg/ m²/day divided q12h</td>
<td>Blurred vision, nausea, decrease in contractility, proarrhythmia</td>
<td>Amiodarone increases toxicity</td>
<td>0.2-1 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>SVT, atrial tachycardia, atrial fibrillation, VT</td>
<td>Oral: 150-300 mg/m²/24 hr divided q6h</td>
<td>Hypotension, decreased contractility, hepatic toxicity, paresthesia, headache, proarrhythmia</td>
<td>Increases digoxin levels</td>
<td>0.2-1 µg/mL</td>
<td></td>
</tr>
</tbody>
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Continued
<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATIONS</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
<th>DRUG INTERACTIONS</th>
<th>DRUG LEVEL</th>
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<tbody>
<tr>
<td><strong>CLASS II: β-BLOCKERS</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>SVT, long QT</td>
<td>Oral: 1-4 mg/kg/24 hr divided q6h</td>
<td>Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF</td>
<td>Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function</td>
<td></td>
</tr>
<tr>
<td>Max dose 60 mg/24 hr</td>
<td>IV: 0.1-0.15 mg/kg over 5 min</td>
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<tr>
<td>Max IV dose: 10 mg</td>
<td></td>
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</tr>
<tr>
<td>Atenolol</td>
<td>SVT</td>
<td>Oral: 0.5-1 mg/kg/24 hr once daily or divided q12h</td>
<td>Bradycardia, loss of concentration, school performance problems</td>
<td>Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>SVT, long QT</td>
<td>Oral: 1-2 mg/kg/24 hr given once daily</td>
<td>Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF</td>
<td>Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS III: PROLONGS REPOLARIZATION</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>SVT, JET, VT</td>
<td>Oral: 10 mg/kg/24 hr in 1-2 divided doses for 4-14 days; reduce to 5 mg/kg/24 hr for several weeks; if no recurrence, reduce to 2.5 mg/kg/24 hr</td>
<td>Hypothyroidism or hyperthyroidism, elevated triglycerides, hepatic toxicity, pulmonary fibrosis</td>
<td>Digoxin (increases levels), flecainide, procainamide, quinidine, warfarin, phenytoin</td>
<td>0.5-2.5 mg/L</td>
</tr>
<tr>
<td>IV: 2.5-5 mg/kg over 30-60 min, may repeat 3 times, then 2-10 mg/kg/24 hr continuous infusion</td>
<td></td>
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<tr>
<td><strong>CLASS IV AND MISCELLANEOUS MEDICATIONS</strong></td>
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<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>SVT (not WPW), atrial flutter, atrial fibrillation</td>
<td>Oral/load instructions: Premature: 20 µg/kg Newborn: 30 µg/kg &gt;6 mo: 40 µg/kg</td>
<td>PAC, PVC, bradycardia, AV block, nausea, vomiting, anorexia, prolongs PR interval</td>
<td>Quinidine Amiodarone, verapamil, increase digoxin levels</td>
<td>1-2 mg/mL</td>
</tr>
<tr>
<td>Give ( \frac{1}{3} ) total dose followed by ( \frac{1}{3} \times 8-12h \times 2 ) doses Maintenance: 10 µg/kg/24 hr divide q12h Max dose: 0.5 mg</td>
<td></td>
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</tr>
<tr>
<td>IV: ( \frac{1}{3} ) PO dose Max dose: 0.5 mg</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Verapamil</td>
<td>SVT (not WPW)</td>
<td>Oral: 2-7 mg/kg/24 hr divided q8h</td>
<td>Bradycardia, asystole, high degree AV block, PR prolongation, hypotension, CHF</td>
<td>Use with β-blocker or disopyramide exacerbates CHF, increases digoxin level and toxicity</td>
<td></td>
</tr>
<tr>
<td>Max dose: 480 mg</td>
<td>IV: 0.1-0.2 mg/kg q 20 min x 2 doses Max dose: 5-10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>SVT</td>
<td>IV: 50-300 µg/kg by need rapid IV push Begin with 50 µg/kg and increase by 50-100 µg/kg/dose Max dose: 18 mg</td>
<td>Chest pain, flushing, dyspnea, bronchospasm, atrial fibrillation, bradycardia, asystole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Premature atrial contractions are common in childhood, usually in the absence of cardiac disease. Depending on the degree of prematurity of the beat (coupling interval) and the preceding R-R interval (cycle length), premature atrial complexes may result in a normal, a prolonged (aberrancy), or an absent (blocked premature atrial complex) QRS complex. The last occurs when the premature impulse cannot conduct to the ventricle due to refractoriness of the AV node or distal conducting system (Fig. 435-3). Atrial extrasystoles must be distinguished from premature ventricular contractions (PVCs). Careful scrutiny of the electrocardiogram for a premature P wave preceding the QRS will either show a premature P wave superimposed on, and deforming, the preceding T wave, or a P wave that is premature and has a different contour from that of the other sinus P waves. Atrial premature complexes usually reset the sinus node pacemaker, leading to an incomplete compensatory pause, but this feature is not regarded as a reliable means of differentiating atrial from ventricular premature complexes in children.

PVCs may arise in any region of the ventricles. They are characterized by premature, widened, bizarre QRS complexes that are not preceded by a premature P wave (Fig. 435-4). When all premature beats have identical contours, they are classified as uniform, suggesting origin from a common site. When PVCs vary in contour, they are designated as multiform, suggesting origin from more than one ventricular site. Ventricular extrasystoles are often, but not always, followed by a full compensatory pause. The presence of fusion beats, that is, complexes with morphologic features that are intermediate between those of normal sinus beats and those of PVCs, proves the ventricular origin of the premature beat. Extrasystoles produce a smaller stroke and pulse volume than normal and, if quite premature, may not be audible with a stethoscope or palpable at the radial pulse. When frequent, extrasystoles may assume a definite rhythm, for example, alternating with normal beats (bigeminy) or occurring after 2 normal beats (trigeminy). Most patients are unaware of single PVCs, although some may be aware of a “skipped beat” over the precordium. This sensation is caused by the increased stroke volume of the normal beat after a compensatory pause. Anxiety, a febrile illness, or ingestion of various drugs or stimulants may exacerbate PVCs.

**Figure 435-3** Premature atrial contraction (PAC). QRS complexes—the 8th, 10th, and final—in this strip are preceded by a P wave that is inverted, indicative of an ectopic origin of atrial depolarization. Note that the 8th and final QRS complexes resemble those of sinus origin, whereas the 10th is aberrantly conducted. This shift in origin is a function of the preceding cycle length, which influences the refractory period of the bundle branches. The fact that the pause after the PAC is longer than 2 P-P intervals implies that the premature atrial depolarization has invaded and discharged the sinus node and then reset it so that it fires later.

**Figure 435-4** Premature ventricular contractions in a bigeminal rhythm, in a patient who is hyperventilating. Note that the premature beat is wide and has a completely different morphology from that of the sinus beat. The premature beat is not preceded by a discernible premature P wave or any appreciable deformation of the preceding T wave.
It is important to distinguish PVCs that are benign from those that are likely to lead to more severe arrhythmias. The former usually disappear during the tachycardia of exercise. If they persist or become more frequent during exercise, the arrhythmia may have greater significance. The following criteria are indications for further investigation of PVCs that could require suppressive therapy: (1) 2 or more ventricular premature beats in a row; (2) multiform PVCs; (3) increased ventricular ectopic activity with exercise; (4) R-on-T phenomenon (premature ventricular depolarization occurs on the T wave of the preceding beat); (5) extreme frequency of beats (e.g., >20% of total beats on Holter monitoring); and (6) most importantly, the presence of underlying heart disease, a history of heart surgery, or both. The best therapy for benign PVCs is reassurance that the arrhythmia is not life threatening, although very symptomatic individuals may benefit from suppressive therapy. Malignant PVCs are usually secondary to another medical problem (electrolyte imbalance, hypoxia, drug toxicity, or cardiac injury). Successful treatment includes correction of the underlying abnormality. An intravenous lidocaine bolus and drip is the first line of therapy, with more effective drugs such as amiodarone reserved for refractory cases or for patients undergoing ventricular dysfunction or hemodynamic compromise.

435.3 Supraventricular Tachycardia
George F. Van Hare

Supraventricular tachycardia (SVT) is a general term that includes essentially all forms of paroxysmal or incessant tachycardia except ventricular tachycardia. The category of SVT can be divided into 3 major subcategories: reentrant tachycardias using an accessory pathway, reentrant tachycardias without an accessory pathway, and ectopic or automatic tachycardias. Atioventricular reciprocating tachycardia (AVRT) involves an accessory pathway and is the most common mechanism of SVT in infants. Atioventricular node reentry tachycardia (AVNRT) is rare in infancy but there is an increasing incidence of AVNRT in childhood and into adolescence. Atrial flutter is rarely seen in children with normal hearts, whereas intraatrial reentry tachycardia also known as atrial flutter, is common in patients following cardiac surgery. Atrial flutter and junctional ectopic tachycardias are more commonly associated with abnormal hearts (cardiomyopathy) and in the immediate postoperative period following surgery for congenital heart disease.

CLINICAL MANIFESTATIONS
Reentrant SVT is characterized by an abrupt onset and cessation; it may occur when the patient is at rest or exercising, and in infants it may be precipitated by an acute infection. Attacks may last only a few seconds or may persist for hours. The heart rate usually exceeds 180 beats/min and may occasionally be as rapid as 300 beats/min. The only complaint may be awareness of the rapid heart rate. Many children tolerate these episodes extremely well, and it is unlikely that short paroxysms are a danger to life. If the rate is exceptionally rapid or if the attack is prolonged, precordial discomfort and heart failure may occur. In children, SVT may be exacerbated by exposure to nonprescription decongestants or by bronchodilators.

In young infants, the diagnosis may be more obscure because of the inability to communicate their symptoms. The heart rate at this age is normally higher than in older children and it increases greatly with crying. Infants with SVT on occasion initially present with heart failure, because the tachycardia may go unrecognized for a long time. The heart rate during episodes is frequently in the range of 240-300 beats/min. If the attack lasts 6-24 hr or more, heart failure may be recognized, and the infant will have an ashen color, and be restless and irritable, with tachypnea, poor pulses and hepatomegaly. When tachycardia occurs in the fetus, it can cause hydrops fetalis, which is the in utero manifestation of heart failure.

In neonates, SVT is usually manifested as a narrow QRS complex (<0.08 sec). The P wave is visible on a standard electrocardiogram in only 50-60% of neonates with SVT, but it is detectable with a transesophageal lead in most patients. Differentiation from sinus tachycardia may be difficult, but is important, as sinus tachycardia requires treatment of the underlying problem (e.g., sepsis, hypovolemia) rather than antiarrhythmic medication. If the rate is >230 beats/min with an abnormal P-wave axis (a normal P wave is positive in leads I and aVF), sinus tachycardia is not likely. The heart rate in SVT also tends to be relatively unvarying, whereas in sinus tachycardia the heart rate varies with changes in vagal and sympathetic tone. AV reciprocating tachycardia uses a bypass tract that may either be able to conduct bidirectionally (Wolff-Parkinson-White [WPW] syndrome) or retrograde only (concealed accessory pathway). Patients with WPW syndrome have a small, but real risk of sudden death. If the accessory pathway rapidly conducts in antegrade fashion, the patient is at risk for atrial fibrillation begetting ventricular fibrillation. Risk stratification, including 24 hr Holter monitoring and exercise study, may help differentiate patients at higher risk for sudden death from WPW. Syncope is an ominous symptom in WPW and any patient with syncope and WPW syndrome should have an electrophysiology study and likely catheter ablation.

The typical electrocardiographic features of the WPW syndrome are seen when the patient is not having tachycardia. These features include a short P-R interval and slow upstroke of the QRS (delta wave) (Fig. 435-5). Although most often present in patients with a normal heart, this syndrome may also be associated with Ebstein anomaly of the tricuspid valve, or hypertrophic cardiomyopathy. The critical anatomic structure is an accessory pathway consisting of a muscular bridge connecting atrium to ventricle on either the right or the left side of the AV ring (Fig. 435-6). During sinus rhythm, the impulse is carried over both the AV node and the accessory pathway; it produces some degree of fusion of the 2 depolarization fronts that results in an abnormal QRS. During AVRT, an impulse is carried in antegrade fashion through the AV node (orthodromic tachycardia), which results in a normal QRS complex, and in retrograde fashion
through the accessory pathway to the atrium, thereby perpetuating the tachycardia. In these cases, only after cessation of the tachycardia is the typical ECG features of WPW syndrome recognized (see Fig. 435-5). When rapid antegrade conduction occurs through the accessory pathway during tachycardia and the retrograde re-entry pathway to the atrium is via the AV node (antidromic tachycardia), the QRS complexes are wide and the potential for more serious arrhythmias (ventricular fibrillation) is greater, especially if atrial fibrillation occurs.

AVNRT involves the use of 2 pathways within the AV node, so-called slow and fast AV node pathways. This arrhythmia is more commonly seen in adolescence. It is one of the few forms of SVT that is occasionally associated with syncope. This arrhythmia is often seen in association with exercise.

**TREATMENT**

Vagal stimulation by placing of the face in ice water (in older children) or by placing an ice bag over the face (in infants) may abort the attack. To terminate the attack, older children may be taught vagal maneuvers such as the Valsalva maneuver, straining, breath holding, or standing on their head. Ocular pressure must never be performed, and carotid sinus massage is very rarely effective. When these measures fail, several pharmacologic alternatives are available (see Table 435-1). In stable patients, adenosine by rapid intravenous push is the treatment of choice because of its rapid onset of action and minimal effects on cardiac contractility. The dose may need to be increased if no effect on the tachycardia is seen. Because of the potential for adenosine to initiate atrial fibrillation, it should never be administered without a means for direct current (DC) cardioversion near at hand. Calcium channel blockers such as verapamil have also been used in the initial treatment of SVT in older children. Verapamil may reduce cardiac output and produce hypotension and cardiac arrest in infants younger than 1 yr; it is, therefore, contraindicated in this age group. In urgent situations when symptoms of severe heart failure have already occurred, synchronized DC cardioversion (0.5-2 J/kg) is recommended as the initial management (see Chapter 67).

Once the patient has been converted to sinus rhythm, a long-acting agent may be selected for maintenance therapy. In patients without an antegrade accessory pathway (non-WPW), the β-blockers are the mainstay of drug therapy. Digoxin is also popular and may be effective in infants, but less so in older children. In children with WPW, digoxin or calcium channel blockers may increase the rate of antegrade conduction of impulses through the bypass tract, with the possibility of ventricular fibrillation, and are therefore contraindicated. These patients are usually managed with β-blockers. In patients with resistant tachycardias, flecainide, propafenone, sotalol, and amiodarone have all been used. Most antiarrhythmic agents have the potential of causing new dangerous arrhythmias (proarrhythmia) and decreasing heart function. Flecainide and propafenone in particular should be limited to use in patients with otherwise normal hearts.

If cardiac failure occurs because of prolonged tachycardia in an infant with a normal heart, cardiac function usually returns to normal after sinus rhythm is reinstated, although it may take days to weeks. Infants with SVT diagnosed within the 1st 3-4 mo of life have a lower incidence of recurrence than do those in whom it is initially diagnosed at a later age. These patients have an 80% chance of resolution by the 1st yr of life, although approximately 30% will have recurrences later in childhood; if medical therapy is required, it can be tapered within a year and the patient watched for signs of recurrence. Parents should be taught to measure the heart rate in their infants, so that prolonged unapparent episodes of SVT may be detected before heart failure occurs.

**Twenty-four hour electrocardiographic (Holter) recordings** are useful in monitoring the course of therapy and in detecting brief runs of asymptomatic tachycardia, particularly in younger children and infants. Some centers use transesophageal pacing to evaluate the effects of therapy in infants. More detailed electrophysiologic studies performed in the cardiac catheterization laboratory are often indicated in patients with refractory SVTs who are candidates for catheter ablation. During an electrophysiologic study, multiple electrode catheters are placed transvenously in different locations in the heart. Pacing is performed to evaluate the conduction characteristics of the accessory pathway and to initiate the tachyarrrhythmia, and mapping is performed to locate the accessory pathway. Catheter ablation of an accessory pathway is frequently used in children and teenagers, as well as in patients who require multiple agents or find drug side effects intolerable or for whom arrhythmia control is poor. Ablation may be performed either by radiofrequency ablation, which creates tissue heating, or cryoablation, in which tissue is frozen (Fig. 435-7). The overall initial success rate for catheter ablation ranges from approximately 90-98%, depending on the location of the accessory pathway. Surgical ablation of bypass tracts is only rarely done, and is proposed only in carefully selected patients.

The management of SVT caused by AVNRT is nearly identical to that for AVRT. Children with AVNRT are not at increased risk of sudden death, as they do not have a manifest accessory pathway. In practice, their episodes are more likely to be brought on by exercise or other forms of stress, and the heart rates can be quite fast, leading to chest pain, dizziness, and, occasionally, syncope. If chronic antiarritmic medication is desired, β-blockers are the drugs of choice; acutely, AVNRT responds to adenosine. Less is known about the natural history, but patients with AVNRT are seen quite commonly in adulthood, so spontaneous resolution seems unlikely. Patients are quite amenable to catheter ablation, either using radiofrequency energy or cryoablation, with high success rates and low complication rates.

**Atrial ectopic tachycardia** is an uncommon tachycardia in childhood. It is characterized by a variable rate (seldom >200 beats/min), identifiable P waves with an abnormal axis, and either a sustained or incessant nonsustained tachycardia. This form of atrial tachycardia has a single automatic focus. Identification of this mechanism is aided by monitoring the electrocardiogram while initiating vagal or pharmacologic therapy. Reentry tachycardias “break” suddenly, whereas automatic tachycardias gradually slow down and then gradually speed up again. Atrial ectopic tachycardias are usually more difficult to control pharmacologically than are the more common reentrant tachycardias. If pharmacologic therapy with a single agent is unsuccessful, catheter ablation is suggested and has a success rate >90%.

**Chaotic or multifocal atrial tachycardia** is defined as atrial tachycardia with 23 ectopic P waves, frequent blocked P waves, and varying P-R intervals of conducted beats. This arrhythmia occurs most often in infants younger than 1 yr, usually without cardiac disease, although some evidence suggests an association with viral myocarditis or pulmonary disease. The goal of drug treatment is slowing of...
the ventricular rate, as conversion to sinus may not be possible, and multiple agents are often required. When this arrhythmia occurs in infancy, it usually terminates spontaneously by 3 yr of age.

**Accelerated junctional ectopic tachycardia (JET)** is an automatic (non-reentry) arrhythmia in which the junctional rate exceeds that of the sinus node and AV dissociation results. This arrhythmia is most often recognized in the early postoperative period after cardiac surgery and may be extremely difficult to control. Reduction of the infusion rate of catecholamines and control of fever are important adjuncts to management. Congenital JET may be seen in the absence of surgery. It is incessant, and can lead to dilated cardiomyopathy. Intravenous amiodarone is effective in the treatment of postoperative JET. Patients who require chronic therapy may respond to amiodarone or sotalol. Congenital JET can be cured by catheter ablation, but long-term AV block requiring a pacemaker is a prominent complication.

**Atrial flutter**, also known as **intraatrial reentrant tachycardia**, is an atrial tachycardia characterized by atrial activity at a rate of 250-300 beats/min in children and adolescents, and 400-600 beats/min in neonates. The mechanism of common atrial flutter consists of a reentrant or rhythm originating in the right atrium circling the tricuspid valve annulus. Because the AV node cannot transmit such rapid impulses, some degree of **AV block** is virtually always present, and the ventricles respond to every 2nd to 4th atrial beat (Fig. 435-8). Occasionally, the response is variable and the rhythm appears irregular.

In older children, atrial flutter usually occurs in the setting of congenital heart disease; neonates with atrial flutter frequently have normal hearts. Atrial flutter may occur during acute infectious illnesses but is most often seen in patients with large stretched atria, such as those associated with long-standing mitral or tricuspid insufficiency, tricuspid atresia, Ebstein anomaly, or rheumatic mitral stenosis. Atrial flutter can also occur after palliative or corrective intra-atrial surgery. Uncontrolled atrial flutter may precipitate heart failure. Vagal maneuvers or adenosine may produce a temporary slowing of the heart rate as a result of increased AV block, allowing a diagnosis to be made. The **diagnosis** is confirmed by electrocardiography, which demonstrates the rapid and regular atrial sawtoothed flutter waves. Atrial flutter usually converts immediately to sinus rhythm by **synchronized DC cardioversion**, which is most often the **treatment of choice**. Patients with chronic atrial flutter in the setting of congenital heart disease may be at increased risk for **thromboembolism** and stroke and should thus undergo anticoagulation before elective cardioversion. β-blockers or calcium channel blockers may be used to slow the ventricular response.

**Figure 435-7** Three-dimensional electroanatomical mapping of focal atrial tachycardias. Focal site of early activation (red) is shown, with radial propagation away from that central site. The activation map was superimposed onto the patient’s cardiac CT scan, taken before the procedure and imported into the mapping system. **A,** Earliest site of activation, mapped to the posterior aspect of the LSPV ostium. Posterior external view (left side) and endoluminal or internal view looking from within the left atrium into the mouth of the LSPV (right side) are shown. **B,** Earliest site mapped to the aortomitral continuity. The anatomic relation between the mitral annulus and the aortic root can be clearly appreciated (left side). The location of the ablation catheter at the site of earliest atrial activation during atrial tachycardia is shown on the TEE image (right side). AMC, aortomitral continuity; AoV, aortic valve; LA, left atrium; LAA, left atrial appendage; LAO, left anterior oblique; LIPV, left inferior pulmonary veins; LMCA, left main coronary artery; LSPV, left superior pulmonary vein; LV, left ventricle; MV, mitral valve; RIPV, right inferior pulmonary veins; RSPV, right superior pulmonary vein; TEE, transesophageal echocardiogram. (From Lee G, Sanders P, Kalman JM: Catheter ablation of atrial arrhythmias: state of the art. Lancet 380:1509–1518, 2012, Fig 3.)
in atrial flutter by prolonging the AV node refractory period. Other agents may be used to maintain sinus rhythm, and choices include Class I agents such as procainamide or propafenone, Class III agents such as amiodarone and sotalol. Catheter ablation has been used in patients with normal hearts and those with congenital heart disease with moderate success. Following cardioversion, neonates with normal hearts may be followed or may be treated with digoxin or propranolol for 6–12 mo, after which the medication can usually be discontinued, as neonatal atrial flutter generally does not recur.

Atrial fibrillation is uncommon in children and is rare in infants. The atrial excitation is chaotic and more rapid (400–700 beats/min) and produces an irregularly irregular ventricular response and pulse (Fig. 435–9). This rhythm disorder is often associated with atrial enlargement or disease. Atrial fibrillation may be seen in older children with rheumatic mitral valve stenosis. It is also seen rarely as a complication of atrial surgery, in patients with left atrial enlargement secondary to left AV valve insufficiency, and in patients with WPW syndrome. Thyrotoxicosis, pulmonary embolism, pericarditis, or cardiomyopathy may be suspected in a previously normal older child or adolescent with atrial fibrillation. Very rarely, atrial fibrillation may be familial. The best initial treatment is rate control, most effectively with calcium channel blockers, to limit the ventricular rate during atrial fibrillation. Digoxin is not given if WPW syndrome is present. Normal sinus rhythm may be restored with intravenous procainamide, ibutilide or amiodarone, or by DC cardioversion, and DC cardioversion is the first choice in hemodynamically unstable patients. Patients with chronic atrial fibrillation are at risk for the development of thromboembolism and stroke and should undergo anticoagulation with warfarin. Patients being treated by elective cardioversion should also undergo anticoagulation.

### 435.4 Ventricular Tachyarrhythmias

*George F. Van Hare*

Ventricular tachycardia (VT) is less common than SVT in pediatric patients. VT is defined as at least 3 PVCs at >120 beats/min (Fig. 435-10). It may be paroxysmal or incessant. VT may be associated with myocarditis, anomalous origin of a coronary artery, arrhythmogenic right ventricular dysplasia, mitral valve prolapse, primary cardiac tumors, and dilated or hypertrophic cardiomyopathy. It is seen with prolonged QT interval of either congenital or acquired (proarrhythmic drugs) causation, WPW syndrome, and drug use (cocaine, amphetamines). It may develop years after intraventricular surgery (especially tetralogy of Fallot and related defects) or occur without obvious organic heart disease. VT must be distinguished from SVT with aberrancy or rapid conduction over an accessory pathway (Table 435-2). The presence of clear capture and fusion beats confirms the diagnosis of VT. Although some children tolerate rapid ventricular rates for many hours, this arrhythmia should be promptly treated because hypotension and degeneration into ventricular fibrillation may result. For patients who are hemodynamically stable, intravenous amiodarone, lidocaine, or procainamide are the initial drugs of choice. If treatment is to be successful, it is critical to search for and correct any underlying abnormalities such as electrolyte imbalance, hypoxia, or drug toxicity. Amiodarone is the treatment of choice during cardiac arrest (see Chapter 67). Hemodynamically unstable patients with VT should be immediately treated with DC cardioversion. Overdrive ventricular pacing, through temporary pacing wires or a permanent pacemaker, may also be effective, although it may cause the arrhythmia to deteriorate into ventricular fibrillation. In the neonatal period, VT may be associated with an anomalous left coronary artery (see Chapter 432.2) or a myocardial tumor.

Unless a clearly reversible cause is identified, electrophysiologic study is usually indicated for patients in whom VT has developed, and depending on the findings, catheter ablation and/or ICD implantation may be indicated.

A related arrhythmia, ventricular accelerated rhythm, is occasionally seen in infants. It is defined the same way as VT, but the rate is only slightly faster than the coexisting sinus rate (within 10%). It is generally benign and resolves spontaneously.

Ventricular fibrillation is a chaotic rhythm that results in death unless an effective ventricular beat is rapidly re-established (see Fig. 435-10). Usually, cardiopulmonary resuscitation and DC defibrillation are necessary. If defibrillation is ineffective or fibrillation recurs, amiodarone or lidocaine may be given intravenously and defibrillation repeated (see Chapter 67). After recovery from ventricular fibrillation, a search should be made for the underlying cause. Electrophysiologic study is indicated for patients who have survived
ventricular fibrillation unless a clearly reversible cause is identified. If WPW syndrome is noted, catheter ablation should be performed. For patients in whom no correctable abnormality can be found, an ICD is nearly always indicated, because of the high risk of sudden death.

### 435.5 Long QT Syndromes

**George F. Van Hare**

Long QT syndromes (LQTS) are genetic abnormalities of ventricular repolarization, with an estimated incidence of about 1 per 10,000 births (Table 435-3). They present as a long QT interval on the surface electrocardiogram and are associated with malignant ventricular arrhythmias (torsades de pointes and ventricular fibrillation). They are a cause of syncope and sudden death and may be the cause of some cases of sudden infant death syndrome, drowning, and intrauterine fetal demise. In perhaps 80% of cases, there is an identifiable genetic mutation. The old distinction between dominant and recessive forms of the disease (Romano-Ward syndrome vs. Jervell-Lange-Nielsen syndrome) is no longer made, as the latter recessive condition is known to be a result of the homozygous state. Jervell-Lange-Nielsen syndrome is associated with congenital sensorineural deafness. Asymptomatic but at-risk patients carrying the gene mutation may not all have a
Acquired Causes of QT Prolongation*

<table>
<thead>
<tr>
<th>DRUGS</th>
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<tbody>
<tr>
<td>Antibiotics—erythromycin, clarithromycin, azithromycin, telithromycin, trimethoprim/sulfamethoxazole, fluoroquinolones†</td>
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<td>Antifungal agents—fluconazole, itraconazole, ketoconazole</td>
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<td>Antiprotozoal agents—pentamidine isethionate</td>
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<td>Antihistamines—astemizole, terfenadine (Seldane; Seldane has been removed from the market for this reason)</td>
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<tr>
<td>Antidepressants—tricyclics such as imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), and doxepin (Sinequan)</td>
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<tr>
<td>Antipsychotics—haloperidol, risperidone, phenothiazines such as thioridazine (Mellaril) and chlorpromazine (Thorazine), selective serotonin uptake inhibitors</td>
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<td>Antiarrhythmic agents</td>
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<tr>
<td>Class IA (sodium channel blockers)—quinidine, procainamide, disopyramide</td>
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<tr>
<td>Class III (prolong depolarization)—amiodarone (rare), bretylium, dofetilide, N-acetyl-procainamide, sotalol</td>
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<td>Lipid-lowering agents—probufol</td>
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<td>Antianginals—bepridil</td>
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<tr>
<td>Diuretics (through K⁺ loss)—furosemide (Lasix), ethacrynic acid (bumetanide [Bumex])</td>
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<td>Opiates—methadone, oxycodeone</td>
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<td>Oral hypoglycemic agents—glibenclamide, glyburide</td>
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<td>Motility agents—cisapride, domperidone</td>
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<td>Vasodilators—prenylamine</td>
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<th>ELECTROLYTE DISTURBANCES</th>
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<tr>
<td>Bradycardia—complete atrioventricular block, severe bradycardia, sick sinus syndrome</td>
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<td>Myocardial dysfunction—anthracycline cardiotoxicity, congestive heart failure, myocarditis, cardiac tumors</td>
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<td>Endocrinopathy—hyperparathyroidism, hypothyroidism, pheochromocytoma</td>
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<tr>
<td>Neurologic—encephalitis, head trauma, stroke, subarachnoid hemorrhage</td>
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<tr>
<td>Nutritional—alcoholism, anorexia nervosa, starvation</td>
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*Table 435-4: Acquired Causes of QT Prolongation*

### Prolonged QT Duration

Prolonged QT duration. QT interval prolongation may become apparent with exercise or during catecholamine infusions.

Genetic studies have identified mutations in cardiac potassium and sodium channels (see Table 435-3). Additional forms (up to 13 variants) of LQTS have been described, but these are much more uncommon. Genotype may predict clinical manifestations; for example, LQT1 events are usually stress induced, whereas events in LQT3 often occur during sleep. LQT2 events have an intermediate pattern. LQT3 has the highest probability for sudden death, followed by LQT2 and then LQT1. Drugs may prolong the QT interval directly but more often do so when drugs such as erythromycin or ketoconazole inhibit their metabolism (Table 435-4).

The clinical manifestation of LQTS in children is most often a syncopal episode brought on by exercise, fright, or a sudden startle; some events occur during sleep (LQT3). Patients can initially be seen with seizures, presyncope, or palpitations; approximately 10% are initially in cardiac arrest. The diagnosis is based on electrocardiographic and clinical criteria. Not all patients with long QT intervals have LQTS, and patients with normal QT intervals on a resting electrocardiogram may have LQTS. A heart rate–corrected QT interval of >0.47 sec is highly indicative, whereas a QT interval of >0.44 sec is suggestive. Other features include notched T waves in 3 leads, T-wave alternans, a low heart rate for age, a history of syncope (especially with stress), and a familial history of either LQTS or unexplained sudden death. Twenty-four hour Holter monitoring and exercise testing are adjuncts to the diagnosis. Genotyping is available and can identify the mutation in approximately 80% of patients known to have LQTS by clinical criteria. Genotyping is not useful in ruling out the diagnosis in individuals suspected of having the disease, but when positive is very useful in identifying asymptomatic affected relatives of the index case.

### Short QT Syndromes

See Table 435-3 manifest with atrial or ventricular fibrillation and are associated with syncope and sudden death. They are often caused by a gain-of-function mutation in cardiac potassium channels.

Treatment of LQTS includes the use of β-blocking agents at doses that blunt the heart rate response to exercise. Propranolol and nadolol may be more effective than atenolol and metoprolol. Some patients require a pacemaker because of drug-induced bradycardia. In patients with unexplained syncope despite treatment, an implantable cardiac defibrillator is indicated for those who do not respond to β-blocking drugs and those who have experienced cardiac arrest. Genotype-phenotype correlative studies have suggested that β-blocking agents are not effective in patients with LQT3, and in those individuals, an ICD is usually indicated.

### 435.6 Sinus Node Dysfunction

**George F. Van Hare**

Sinus arrest and sinoatrial block may cause a sudden pause in the heartbeat. The former is presumably caused by failure of impulse formation within the sinus node and the latter by a block between the sinus pacemaker complex and the surrounding atrium. These arrhythmias are rare in childhood except in patients who have had extensive atrial surgery.

Sick sinus syndrome is the result of abnormalities in the sinus node or atrial conduction pathways, or both. This syndrome may occur in the absence of congenital heart disease and has been reported in siblings, but it is most commonly seen after surgical correction of congenital heart defects, especially the Fontan procedure and the atrial switch (Mustard or Senning) operation for transposition of the great
artefacts. Clinical manifestations depend on the heart rate. Most patients remain asymptomatic without treatment, but dizziness and syncope can occur during periods of marked sinus slowing with failure of junctional escape (Fig. 435-11). Pacemaker therapy is indicated in patients who experience symptoms such as exercise intolerance or syncope.

Patients with sinus node dysfunction may also have episodes of SVT ("tachy-brady syndrome") with symptoms of palpitations, exercise intolerance, or dizziness. Treatment must be individualized. Drug therapy to control tachyarrhythmias (propranolol, sotalol, amiodarone) may suppress sinus and AV node function to such a degree that further symptomatic bradycardia may be produced. Therefore, insertion of a pacemaker in conjunction with drug therapy is usually necessary for such patients, even in the absence of symptoms ascribable to low heart rate.

435.7 AV Block

**George F. Van Hare**

AV block may be divided into 3 forms. In 1st-degree AV block, the PR interval is prolonged, but all the atrial impulses are conducted to the ventricle (Fig. 435-12). In 2nd-degree AV block, not every atrial impulse is conducted to the ventricle. In the variant of 2nd-degree block known as the Wenckebach type (also called Mobitz type I), the PR interval increases progressively until a P wave is not conducted. In the cycle following the dropped beat, the PR interval normalizes (see Fig. 435-12). In Mobitz type II, there is no progressive conduction delay or subsequent shortening of the PR interval after a blocked beat. This conduction defect is less common but has more potential to cause syncope and may be progressive. A related condition is high-grade 2nd-degree AV block, in which 2 or more P waves in a row fail to conduct. This is even more dangerous. In 3rd-degree AV block (complete heart block), no impulses from the atria reach the ventricles (see Fig. 435-12). An independent escape rhythm is usually present, but may not be reliable, leading to symptoms such as syncope.

**Congenital complete AV block** in children is presumed to be caused by autoimmune injury of the fetal conduction system by maternally derived immunoglobulin G antibodies (anti-SSA/Ro, anti-SSB/La) in a mother with overt or, more often, asymptomatic systemic lupus erythematosus or Sjögren syndrome. Autoimmune disease accounts for 60-70% of all cases of congenital complete heart block and ≈80% of cases in which the heart is structurally normal (Fig. 435-13). A mutation of the homeobox gene Nkx2-5 is described in which congenital AV block is seen most commonly in association with atrial septal defects. Complete AV block is also seen in patients with complex congenital heart disease and abnormal embryonic development of the conduction system. It has been associated with myocardial tumors and myocarditis. It is a known complication of myocardial abscess secondary to endocarditis. It is also seen in genetic abnormalities including LQTS and Kearns-Sayre syndrome. It is also a complication of congenital heart disease repair and, in particular, repairs involving ventricular septal defect closure.

The incidence of congenital complete heart block is 1 per 20,000-25,000 live births; a high fetal loss rate may cause an underestimation of its true incidence. In some infants of mothers with systemic lupus erythematosus, complete heart block is not present at birth but develops within the first 3-6 months of age. The arrhythmia is often diagnosed in the fetus (secondary to the dissociation between atrial and ventricular contractions seen on fetal echocardiography) and may produce hydrops fetalis. Maternal treatment with steroids to halt progression or reverse AV block is controversial. Infants with associated congenital heart disease and heart failure have a high mortality rate.

In older children with otherwise normal hearts, the condition is often asymptomatic, although syncope and sudden death may occur. Infants and toddlers may have night terrors, tiredness with frequent naps, and irritability. The peripheral pulse is prominent as a result of the compensatory large ventricular stroke volume and peripheral vasodilation; systolic blood pressure is elevated. Jugular venous pulsations occur irregularly and may be large when the atrium contracts against a closed tricuspid valve (cannon wave). Exercise and atropine may produce an acceleration of ≥10-20 beats/min. Systolic murmurs are frequently audible along the left sternal border, and apical mid-diastolic murmurs are not unusual. The 1st heart sound is variable, as a result of variable ventricular filling with AV dissociation. AV block results in enlagement of the heart on the basis of increased diastolic ventricular filling.

The **diagnosis** is confirmed by electrocardiography; the P waves and QRS complexes have no constant relationship (see Fig. 435-13). The
QRS duration may be prolonged, or it may be normal if the heartbeat is initiated high in the AV node or bundle of His.

The **prognosis** for congenital complete heart block is usually favorable; patients who have been observed to the age of 30-40 yr have lived normal, active lives. Some patients have episodes of exercise intolerance, dizziness, and syncope (Stokes-Adams attacks); this symptom requires the implantation of a permanent cardiac pacemaker. Pacemaker implantation should be considered for patients who develop symptoms such as progressive cardiac enlargement, prolonged pauses, or daytime average heart rates of ≤50 beats/min. In addition, prophylactic pacemaker implantation in adolescents is reasonable considering the low risk of the implant procedure and the difficulty in predicting who will develop sudden severe symptoms.

**Cardiac pacing** is recommended in neonates with low ventricular rates (≤50 beats/min), evidence of heart failure, wide complex rhythms, or congenital heart disease. Isoproterenol, atropine, or epinephrine may be used to try to increase the heart rate temporarily until pacemaker placement can be arranged. Transthoracic epicardial pacemaker implants have traditionally been used in infants; transvenous placement of pacemaker leads is available for young children. Postsurgical complete AV block can occur after any open heart procedure requiring suturing near the AV valves or crest of the ventricular septum. Postoperative heart block is initially managed with temporary pacing wires. The likelihood of a return to sinus rhythm after 10-14 days is low; a permanent pacemaker is recommended after that time.

*Bibliography is available at Expert Consult.*
Sudden death other than sudden infant death syndrome (see Chapter 375) is rare in children younger than 18 yr. Sudden death can be divided into either traumatic or nontraumatic origin. Traumatic causes of sudden death are the most common in children; these include motor vehicle crashes, violent deaths, recreational deaths, and occupational deaths. Nontraumatic sudden deaths are often the result of specific cardiac causes. The incidence of sudden death varies from 0.8-6.2 per 100,000 per year in children and adolescents as opposed to the higher incidence of sudden cardiac death in adults of 1 per 1,000. Approximately 65% of sudden deaths are a result of heart-related problems in patients with either normal or congenitally (corrected, palliated, or unoperated) abnormal hearts. Competitive high-school sports (basketball, football) are high-risk environmental factors. The most common cause of death in competitive athletes is hypertrophic cardiomyopathy, with or without obstruction to left ventricular outflow. Table 436-1 lists other potential causes. These can be classified as structural abnormalities, including aortic stenosis and coronary artery abnormalities; myocardial disease, such as myocarditis; conduction system disease, including long QT syndrome; and miscellaneous causes, including pulmonary hypertension and commotio cordis. Symptoms may be absent before the event but, if present, include syncope, chest pain, dyspnea, and palpitations. Patients may have a family history of heart disease (dilated or hypertrophic cardiomyopathy, long QT interval, arrhythmogenic right ventricular dysplasia, Brugada or Marfan syndromes) or sudden death. Death often follows exertion or exercise.

**MECHANISM OF Sudden Death**

There are 3 mechanisms of sudden death: arrhythmic, nonarrhythmic cardiac (circulatory and vascular causes), and noncardiac. Ventricular fibrillation, while the most common final cause of sudden death in adults, is only the final cause in 10-20% of children with sudden cardiac death. More commonly, bradycardia leads either to ventricular fibrillation or asystole (see Chapter 435).

**CONGENITAL HEART DISEASE**

Valvar aortic stenosis is the congenital defect most commonly associated with sudden death in children. Historically, approximately 5% of children with this disease die, although this has become quite rare in the modern era. A history of syncope, chest pain, and evidence of severe obstruction and left ventricular hypertrophy are risk factors (see Chapter 434.5). Coronary artery anomalies are also commonly associated with sudden death in children and adolescents. The most common abnormality associated with sudden death is the origin of the left main coronary artery from the right sinus of Valsalva. The coronary artery therefore courses between the aorta and pulmonary artery, and may also be intramural in course. Exercise results in a rise in pulmonary and aortic pressure, and this is thought to compress the left main coronary artery and results in ischemia due to compression or kinking. Anomalous origin of the right coronary artery from the left sinus of Valsalva is much more common, but only rarely is a cause of sudden death.

**CARDIOMYOPATHY**

All 3 major types of cardiomyopathy (hypertrophic, dilated, and restrictive) are associated with sudden death in the pediatric population; sudden death may be the initial manifestation of the cardiomyopathy (see Chapter 439). Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in the athletic adolescent. The annual risk of sudden death in young patients with HCM is 2% per year. Risk factors for sudden death include a family history of sudden death, symptoms, ventricular arrhythmias, and presentation at an early age. Many patients with HCM have obstruction to the left ventricular outflow tract. The mechanism of sudden death is arrhythmic and may be secondary to development of dynamic obstruction with exercise and resultant loss of cardiac output, or may be related to cardiac ischemia. Thus, patients without left ventricular outflow tract obstruction are also at risk of sudden death. The dilated cardiomyopathies are also associated with sudden cardiac death in children, although the risk is clearly lower than in adults.

Arrhythmogenic right ventricular dysplasia is a specific form of cardiomyopathy associated with exercise-induced ventricular arrhythmias and sudden death. The diagnosis can be difficult; MRI, electrophysiology study, or endomyocardial biopsy is used with limited reliability. Pathology includes transmural fatty replacement of right ventricular myocardium, with patchy areas of fibrosis. Myocarditis has been found commonly on pathology of patients with sudden death of unknown etiology. Symptoms prior to sudden death may be absent, or may include overt heart failure or subtle findings such as a high heart rate. Pediatric patients may have complete heart block or ventricular arrhythmias with this disease.

**CARDIAC ARRHYTHMIA**

A primary conduction system abnormality may result in sudden death. Causes include Wolff-Parkinson-White (WPW) syndrome, long QT syndrome, and Brugada syndrome. Besides causing supraventricular tachycardia, WPW syndrome can result in atrial fibrillation with rapid conduction across the accessory pathway leading to ventricular fibrillation and sudden death (Fig. 436-1). This is unusual in pediatric patients but has an increasing incidence in adolescence. In adults, there is an incidence of sudden death in asymptomatic patients of 1 per 1,000 patient-years, but this rate may well be higher in children, who by definition have not survived to adulthood. As digoxin and verapamil can augment conduction down accessory pathways, these drugs are contraindicated in WPW syndrome. Long QT syndrome (see Chapter 435), a group of channelopathies that affect ventricular repolarization, is also associated with sudden death.
The mechanism of sudden death is polymorphic ventricular tachycardia (torsades de pointes) (Fig. 436-3). An initial presentation of sudden cardiac death is found in 9% of patients. Thus, treatment of asymptomatic patients with a long QT interval on electrocardiogram (ECG) and positive family history is advised. Acquired long QT intervals may be seen in patients with marked electrolyte abnormalities, central nervous system injury, or starvation (including bulimia and anorexia nervosa). Medications can also result in prolongation of the QT interval (see Table 435-4 in Chapter 435). These patients are also at risk of malignant ventricular arrhythmias, and correction of the underlying problem may be necessary to reduce the risk of sudden death.

Brugada syndrome, an autosomal dominant disorder, caused in approximately 30% of patients to a mutation in the SCN5A gene, is associated with sudden cardiac death, often associated with fever, drugs, nighttime electrolyte disorders, or after a large meal (see Fig. 436-4). Typical ECG findings include coved ST segment elevations in leads V₁-V₃; death results from either ventricular fibrillation or tachycardia.

**MISCELLANEOUS CAUSES**
Commotio cordis is a nearly universally fatal condition that follows blunt nonpenetrating trauma to the chest (e.g., from a baseball or hockey puck). Occasionally, innocent-appearing chest blows incurred at home or at a playground may be fatal. Patients experience immediate ventricular fibrillation in the absence of identifiable cardiac trauma (contusion, hematoma, lacerated coronary artery). Historically death results from ventricular fibrillation that is unresponsive to resuscitative efforts in 85-90% of children. Immediate direct current defibrillation may be necessary to reduce the risk of sudden death.
Of paramount importance is the careful evaluation of any child who experiences syncope in association with exercise, as this may be the last opportunity to diagnose a life-threatening condition in such a patient.

Patient avoidance of high-risk behavior (cocaine use, anorexia nervosa) and knowledge of drug side effects or drug interactions and contraindications is critical. Chest-protecting equipment has not been shown to prevent commotio cordis. Prompt bystander cardiopulmonary resuscitation and rapid defibrillation by an automatic external defibrillator has the best chance of leading to survival. Family survivors of victims of sudden death should be evaluated for genetic causes such as long QT syndrome and HCM.

The use of a preparticipation ECG for the detection of those athletes at risk for sudden death is controversial. Because many athletes either have no pre-event symptoms or are unwilling to admit to symptoms for fear of not being able to play, some have proposed that the ECG may identify a small but at-risk group with HCM or the prolonged QT, Brugada, or WPW syndromes. Preparticipation ECG testing is mandatory in several European countries but not in the United States. If the ECG is positive, echocardiography is performed. Cost-effectiveness studies suggest that the cost for implementation of a national program in the United States would be prohibitive because of the low incidence of sudden death in the pediatric population, the high rate of false-positive ECGs, and the difficulty in definitively excluding cardiac disease in patients with borderline ECG findings. Although studies of regional or national screening programs have suggested some benefit (e.g., the Veneto region of Italy) others have failed to demonstrate any effect of screening on the background incidence of sudden death in young individuals.

EVALUATION AND THERAPY FOR RESUSCITATED PATIENTS

It is important to focus therapy on potentially reversible causes of sudden death. These include correction of major hemodynamic defects, pacing therapy for a patient with bradycardia, or supportive therapy for myocarditis. Unfortunately, reversible causes are not always found in young cardiac arrest survivors. Added to this dilemma is the fact that there is a limited ability to predict antiarrhythmic drug response or risk of recurrence. Thus, the implantable cardioverter defibrillator is the therapy of choice for survivors of arrhythmic sudden death.

MEDICATION FOR ATTENTION-DEFICIT DISORDER

There has been some concern about the possibility that stimulant medications prescribed for the treatment of children with attention-deficit disorder could potentially increase the risk of sudden death. The concern arises from a limited number of reports to the U.S. Food and Drug Administration of sudden death of unknown etiology in individuals taking stimulant medications, most of whom are adults. In a few cases, left ventricular hypertrophy caused by hypertension, coarctation of the aorta, or HCM has been identified at postmortem examination. There are no prospective studies to support the notion that these medications increase the risk, and little or no evidence that electrocardiographic screening will reliably identify a subgroup at risk. Some suggest ECG screening of children prior to starting these medications, but there is no consensus that such an approach is effective.

PREVENTION OF SUDDEN DEATH

The probability of survival to hospital discharge for a young patient who experiences an out-of-hospital cardiac arrest is <20%. The presence of immediate automatic external defibrillators, when combined with standard cardiopulmonary resuscitation at the site of exercise (gym, track, basketball, or football arena), may improve survival substantially. Thus, identifying patients at risk is extremely important.

Many of the more common causes of sudden death in children and adolescents can be identified from the patient’s history (prodromal symptoms), the family history, and physical examination. The American Academy of Pediatrics makes available a downloadable “Preparticipation Physical Evaluation” form that is useful for this purpose (http://www.aap.org). Of paramount importance is the careful evaluation of any child who experiences syncope in association with exercise, as this may be the last opportunity to diagnose a life-threatening condition in such a patient.

Bibliography is available at Expert Consult.
Bibliography


Infective endocarditis includes acute and subacute bacterial endocarditis, as well as nonbacterial endocarditis caused by viruses, fungi, and other microbiologic agents. It is a significant cause of morbidity and mortality in children and adolescents despite advances in the management and prophylaxis of the disease with antimicrobial agents. The inability to eradicate infective endocarditis by prevention or early treatment stems from several factors. The disease represents a complex interplay between a pathogen and host factors such as endothelial disruption and immune function that is still not completely understood; the nature of the infecting organism has changed over time; diagnosis may be difficult during early stages and is thus often delayed until a more serious infection has set in; and special risk groups have emerged, including intravenous drug users; survivors of cardiac surgery, especially those with mechanical prosthesis; patients taking immunosuppressant medications; and patients who require chronic intravascular catheters. Some patients get endocarditis on what was thought to be a previously healthy native valve, although on surgical inspection is found to have mild structural abnormalities.
ETIOLOGY
Virdans-type streptococci (α-hemolytic streptococci) and Staphylococcus aureus remain the leading causative agents for endocarditis in pediatric patients. Other organisms cause endocarditis less frequently and, in ≈6% of cases, blood cultures are negative for any organisms (Table 437-1). No endocarditis should be expected if a child has a normal heart and no underlying disease or trauma. These bacteria include viridans streptococci found in the oral cavity and Actinomyces species. In developing countries, the pathogenic potential of low-grade fever with afternoon elevations, fatigue, myalgia, arthralgia, headache, and, at times, chills, nausea, and vomiting.

NEW or CHANGING HEART MURMURS are common, particularly with associated heart failure. Splenomegaly and petechiae are relatively common.

Table 437-1: Bacterial Agents in Pediatric Infective Endocarditis

<table>
<thead>
<tr>
<th>COMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS</th>
<th>UNCOMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viridans group streptococci (Streptococcus mutans, Streptococcus sanguinis, Streptococcus mitis)</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Group D streptococcus (enterococcus) (Streptococcus bovis, Streptococcus faecalis)</td>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Chlamydia psittaci*</td>
<td>Abiotrophia defectiva (nutritionally variant streptococcus)</td>
</tr>
<tr>
<td>Chlamydia trachomatis*</td>
<td>Coxella burnetti (Q fever)*</td>
</tr>
<tr>
<td>Chlamydia pneumoniae*</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Legionella*</td>
<td>Brucella*</td>
</tr>
<tr>
<td>Bartonella*</td>
<td>Chlamydia pneumoniae*</td>
</tr>
<tr>
<td>Tropheryma whippelii* (Whipple disease)</td>
<td>Legionella*</td>
</tr>
<tr>
<td>HACEK group</td>
<td>Bartonella*</td>
</tr>
<tr>
<td>Streptobacillus moniliformis*</td>
<td>Campylobacter fetus</td>
</tr>
<tr>
<td>Pasteurella multocida*</td>
<td>Culture negative (6% of cases)</td>
</tr>
<tr>
<td>PROSTHETIC VALVE</td>
<td>PROSTHETIC VALVE</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Viridans group streptococcus</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Serratia marcescens</td>
</tr>
<tr>
<td>Diphtheroids</td>
<td>Legionella species*</td>
</tr>
<tr>
<td>Legionella species*</td>
<td>HACEK group</td>
</tr>
<tr>
<td>Fungi*</td>
<td></td>
</tr>
</tbody>
</table>

*These fastidious bacteria plus some fungi may produce culture-negative endocarditis. Detection may require special media, incubation for more than 7 days, polymerase chain reaction on blood or valve for 16SrRNA (bacteria) or 18SrRNA (fungi), or serologic tests.

1 The HACEK group includes Haemophilus species (H. parainfluenzae, H. parainfluenzae, H. aphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella species.

2 Candida species, Aspergillus species, Pseudallescheria boydii, Histoplasma capsulatum.

CLINICAL MANIFESTATIONS
Table 437-2 outlines the manifestations of infective endocarditis.

Early manifestations are usually mild, especially when viridans group streptococci are the infecting organisms. Prolonged fever without other manifestations (except, occasionally, weight loss) that persists for as long as several months may be the only symptom. Alternatively, the onset may be acute and severe, with high, intermittent fever and prostration. Usually, the onset and course vary between these 2 extremes. The symptoms are often nonspecific and consist of low-grade fever with afternoon elevations, fatigue, myalgia, arthralgia, headache, and, at times, chills, nausea, and vomiting. New or changing heart murmurs are common, particularly with associated heart failure. Splenomegaly and petechiae are relatively common.
Serious neurologic complications such as embolic strokes, cerebral abscesses, mycotic aneurysms, and hemorrhage are most often associated with staphylococcal disease and may be late manifestations. Meningitis, increased intracranial pressure, altered sensorium, and focal neurologic signs are manifestations of these complications. Myocardial abscesses may occur with staphylococcal disease and may be late manifestations. Men- can identify the size, shape, location, and mobility of the lesion; when combined with Doppler studies, the presence of valve dysfunction

Identification of infective endocarditis is most often based on a high index of suspicion during evaluation of an infection in a child with an underlying risk factor.

**DIAGNOSIS**

The critical information for appropriate treatment of infective endocarditis is obtained from blood cultures. All other laboratory data are secondary in importance (see Table 437-2). Blood specimens for culture should be obtained as promptly as possible, even if the child feels well and has no other physical findings. Three to 5 separate blood collections should be obtained after careful preparation of the phlebotomy site. Contamination presents a special problem inasmuch as bacteria found on the skin may themselves cause infective endocarditis. The timing of collections is not important because bacteremia can be expected to be relatively constant. In 90% of cases of endocarditis, the causative agent is recovered from the first 2 blood cultures. Bacteremia is low grade in 80% (<100 colony-forming units [CFU]/mL or blood). The laboratory should be notified that endocarditis is suspected so that, if necessary, the blood can be cultured on enriched media for longer than usual (>7 days) to detect nutritionally deficient and fastidious bacteria or fungi. Although bacteremia may occur in the absence of endocarditis, bacteremia secondary to Streptococcus mutans, Streptococcus bovis I, Streptococcus mitior, Streptococcus sanguis, and S. aureus (in the absence of focal musculoskeletal infection) is highly concerning for endocarditis. Antimicrobial pretreatment of the patient reduces the yield of blood cultures to 50-60%. The microbiology laboratory should be notified if the patient has received antibiotics so that more sophisticated methods can be used to recover the offending agent. Other specimens that may be cultured include scrapings from cutaneous lesions, urine, synovial fluid, abscesses, and, in the presence of manifestations of meningitis, cerebrospinal fluid. Serologic diagnostic or polymerase chain reaction of resected valve tissues is necessary in patients with unusual or fastidious microorganisms (Table 437-3; Fig. 437-1).

The index of suspicion should be high when evaluating infection in a child with an underlying contributing factor. The combination of transthoracic and transesophageal echocardiography enhances the ability to diagnose endocarditis. Two-dimensional echocardiography can identify the size, shape, location, and mobility of the lesion; when combined with Doppler studies, the presence of valve dysfunction

<table>
<thead>
<tr>
<th>Table 437-2</th>
<th>Manifestations of Infective Endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HISTORY</td>
<td>Prior congenital or rheumatic heart disease</td>
</tr>
<tr>
<td></td>
<td>Preceding dental, urinary tract, or intestinal procedure</td>
</tr>
<tr>
<td></td>
<td>Intravenous drug use</td>
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<tr>
<td></td>
<td>Central venous catheter</td>
</tr>
<tr>
<td></td>
<td>Prosthetic heart valve</td>
</tr>
<tr>
<td>SYMPTOMS</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>Chest and abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Arthralgia, myalgia</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Malaise, weakness</td>
</tr>
<tr>
<td></td>
<td>Night sweats</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>CNS manifestations (stroke, seizures, headache)</td>
</tr>
<tr>
<td>SIGNS</td>
<td>Elevated temperature</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions)</td>
</tr>
<tr>
<td></td>
<td>Janeway lesions</td>
</tr>
<tr>
<td></td>
<td>New or changing murmur</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli)</td>
</tr>
<tr>
<td></td>
<td>Clubbing</td>
</tr>
<tr>
<td>LABORATORY</td>
<td>Positive blood culture</td>
</tr>
<tr>
<td></td>
<td>Elevated erythrocyte sedimentation rate; may be low with heart or renal failure</td>
</tr>
<tr>
<td></td>
<td>Elevated C-reactive protein</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis</td>
</tr>
<tr>
<td></td>
<td>Immune complexes</td>
</tr>
<tr>
<td></td>
<td>Hypergammaglobulinemia</td>
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<tr>
<td></td>
<td>Hypocomplementemia</td>
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<tr>
<td></td>
<td>Cryoglobulinemia</td>
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<tr>
<td></td>
<td>Rheumatoid factor</td>
</tr>
<tr>
<td></td>
<td>Hematuria</td>
</tr>
<tr>
<td></td>
<td>Renal failure: azotemia, high creatinine (glomerulonephritis)</td>
</tr>
<tr>
<td></td>
<td>Chest radiograph; bilateral infiltrates, nodules, pleural effusions</td>
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<tr>
<td></td>
<td>Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, myocardial abscess, new-onset valve insufficiency</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

<table>
<thead>
<tr>
<th>Table 437-3</th>
<th>Diagnostic Approach to Uncommon Pathogens Causing Endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATHOGEN</td>
<td>DIAGNOSTIC PROCEDURE</td>
</tr>
<tr>
<td>Brucella spp.</td>
<td>Blood cultures; serology; culture, immunohistology, and PCR of surgical material</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>Serology (IgG phase I &gt;1 in 800); tissue culture, immunohistology, and PCR of surgical material</td>
</tr>
<tr>
<td>Bartonella spp.</td>
<td>Blood cultures; serology; culture, immunohistology, and PCR of surgical material</td>
</tr>
<tr>
<td>Chlamydia spp.</td>
<td>Serology; culture, immunohistology, and PCR of surgical material</td>
</tr>
<tr>
<td>Mycoplasma spp.</td>
<td>Serology; culture, immunohistology, and PCR of surgical material</td>
</tr>
<tr>
<td>Legionella spp.</td>
<td>Blood cultures; serology; culture, immunohistology, and PCR of surgical material</td>
</tr>
<tr>
<td>Tropheryma whippelii</td>
<td>Histology and PCR of surgical material</td>
</tr>
</tbody>
</table>

IgG, immunoglobulin G; PCR, polymerase chain reaction.

Figure 437-1 Diagnostic tests applied to clinical specimens for the identification of the causative agents of blood culture–negative endocarditis. Septifast, LightCycler SeptiFast (Roche). Serum should be considered a priority specimen, with Q fever and Bartonella serologic analysis being routinely done. We also suggest that detection of antineuruplan antibodies and rheumatoid factor should be routinely done for diagnosis of noninfective endocarditis. (From Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives. Lancet 379:965–975, 2012, Fig. 2, p. 969.)

(reputarit, obstruction) can be determined and its effect on left ventricular performance quantified. Echocardiography may also be helpful in predicting embolic complications, given that lesions >1 cm and fungating masses are at greatest risk for embolization. The absence of vegetations does not exclude endocarditis, and vegetations are often not visualized in the early phases of the disease or in patients with complex congenital heart lesions.

The Duke criteria help in the diagnosis of endocarditis. Major criteria include (1) positive blood cultures (2 separate cultures for a usual pathogen, 2 or more for less-typical pathogens), and (2) evidence of endocarditis on echocardiography (intracardiac mass on a valve or other site, regurgitant flow near a prosthesis, abscess, partial desiccation of prosthetic valves, or new valve regurgitant flow). Minor criteria include predisposing conditions, fever, embolic-vascular signs, immune complex phenomena (glomerulonephritis, arthritis, rheumatoid factor, Osler nodes, Roth spots), a single, positive blood culture or serologic evidence of infection, and echocardiographic signs not meeting the major criteria. Two major criteria, 1 major and 3 minor, or 5 minor criteria suggest definite endocarditis. A modification of the Duke criteria may increase sensitivity while maintaining specificity. The following minor criteria are added to those already listed: the presence of newly diagnosed clubbing, splenomegaly, splinter hemorhages, and petechiae; a high erythrocyte sedimentation rate; a high C-reactive protein level; and the presence of central nonfeeding lines, peripheral lines, and microscopic hematuria.

PROGNOSIS AND COMPLICATIONS

Despite the use of antibiotic agents, mortality remains high, in the range of 20–25%. Serious morbidity occurs in 50-60% of children with documented infective endocarditis; the most common is heart failure caused by vegetations involving the aortic or mitral valve. Myocardial abscesses and toxic myocarditis may also lead to heart failure without characteristic changes in auscultatory findings and, occasionally, to life-threatening arrhythmias. Systemic emboli, often with central nervous system manifestations, are a major threat. Pulmonary emboli may occur in children with ventricular septal defect or the tetralogy of Fallot, although massive life-threatening pulmonary embolization is rare. Other complications include mycotic aneurysms, rupture of a sinus of Valsalva, obstruction of a valve secondary to large vegetations, acquired ventricular septal defect, and heart block as a result of involvement (abcess) of the conduction system. Additional complications include meningitis, osteomyelitis, arthritis, renal abscess, purulent pericarditis, and immune complex-mediated glomerulonephritis.

TREATMENT

Antibiotic therapy should be instituted immediately once a definitive diagnosis is made. When virulent organisms are responsible, small delays may result in progressive endocardial damage and are associated with a greater likelihood of severe complications. The choice of antibiotics, method of administration, and length of treatment should be coordinated with consultants from both cardiology and infectious diseases (Tables 437-4 and 437-5). Empirical therapy before the identifiable agent is recovered may be initiated with vancomycin plus gentamicin in patients without a prosthetic valve and when there is a high risk of S. aureus, enterococci, or viridans streptococci (the 3 most common organisms). High serum bactericidal levels must be maintained long enough to eradicate organisms that are growing in relatively inaccessible avascular vegetations. Between 5 and 20 times the minimal in vitro inhibiting concentration must be produced at the site of infection to destroy bacteria growing at the core of these lesions. Several weeks are required for a vegetation to organize completely; therapy must be continued through this period so that recrudescence can be avoided. A total of 4–6 wk of treatment is usually recommended. Depending on the clinical and laboratory responses, antibiotic therapy may require modification and, in some instances, more prolonged treatment is required. With highly sensitive viridans group streptococcal infections, shortened regimens that include oral penicillin for some portion have been recommended. In nonstaphylococcal disease, bacteremia usually resolves in 24–48 hr, whereas fever resolves in 5–6 days with appropriate antibiotic therapy. Resolution with staphylococcal disease takes longer.

If the infection occurs on a valve and induces or increases symptoms and signs of heart failure, appropriate therapy should be instituted, including diuretics, afterload reducing agents, and in some cases, digitalis. Surgical intervention for infective endocarditis is indicated for severe aortic, mitral or prosthetic valve involvement with intractable heart failure. Severe heart failure may be associated with acute valve regurgitation, obstruction, or fistula formation. Rarely, a
mycotic aneurysm, rupture of an aortic sinus, intraseptal abscess causing complete heart block, or dehiscence of an intracardiac patch requires an emergency operation. Other surgical indications include failure to sterilize the blood despite adequate antibiotic levels in 7-10 days in the absence of extracardiac infection, myocardial abscess, recurrent emboli, and increasing size of vegetations while receiving therapy. Vegetations (aortic, mitral, prosthetic valve) >10-15 mm are at high risk of embolism. Although antibiotic therapy should be administered for as long as possible before surgical intervention, active infection is not a contraindication if the patient is critically ill as a result of severe hemodynamic deterioration from infective endocarditis. Removal of vegetations and, in some instances, valve replacement may be lifesaving, and sustained antibiotic administration will most often prevent reinfection. Replacement of infected prosthetic valves carries a higher risk.

Fungal endocarditis is difficult to manage and has a poorer prognosis. It has been encountered after cardiac surgery, in severely debilitated or immunosuppressed patients, and in patients on prolonged courses of antibiotics. The drugs of choice are amphotericin B (liposomal or standard preparation) and 5-fluorocytosine. Surgery to excise infected or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or Abiotrophia, Granulicatella, or Gemella spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 µg/mL and trough serum concentration of <1 µg/mL when 3 divided doses are used; nomogram used for single daily dosing.

**PREVENTION**

Recommendations by the American Heart Association for antimicrobial prophylaxis before dental and other surgical procedures received a major revision in 2007. A substantial reduction in the number of patients who require prophylactic treatment and the procedures requiring coverage was recommended. The primary reasons for these revised recommendations were that (1) infective endocarditis is much more likely to result from exposure to the more frequent random bacteremias associated with daily activities than from a dental or surgical procedure; (2) routine prophylaxis may prevent "an exceedingly

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### Table 437-4

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSAGE* AND ROUTE</th>
<th>DURATION, WK</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous crystalline penicillin G sodium</td>
<td>12-18 million U/24 hr IV either continuously or in 4 or 6 equally divided doses</td>
<td>4</td>
<td>Preferred in patients with impairment of 8th cranial nerve function or renal function</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone sodium</td>
<td>2 g/24 hr IV/IM in 1 dose</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pediatric dose:</td>
<td>200,000 U/kg per 24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 hr IV/IM in 1 dose</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Aqueous crystalline penicillin G sodium</td>
<td>12-18 million U/24 hr IV either continuously or in 6 equally divided doses</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
<td>2 wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of &lt;20 mL/min, impaired 8th cranial nerve function, or Abiotrophia, Granulicatella, or Gemella spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 µg/mL and trough serum concentration of &lt;1 µg/mL when 3 divided doses are used; nomogram used for single daily dosing</td>
</tr>
<tr>
<td>Ceftriaxone sodium</td>
<td>2 g/24 hr IV/IM in 1 dose</td>
<td>2</td>
<td></td>
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<tr>
<td>plus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin sulfate†</td>
<td>3 mg/kg per 24 hr IV/IM in 1 dose, or 3 equally divided doses</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pediatric dose:</td>
<td>penicillin 200,000 U/kg per 24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 hr IV/IM in 1 dose; gentamicin 3 mg/kg per 24 hr IV/IM in 1 dose or 3 equally divided doses†</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vancomycin hydrochloride§</td>
<td>30 mg/kg per 24 hr IV in 2 equally divided doses not to exceed 2 g/24 hr unless concentrations in serum are inappropriately low</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pediatric dose:</td>
<td>40 mg/kg per 24 hr IV in 2-3 equally divided doses</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hr after infusion completed) serum concentration of 30-45 µg/mL and a trough concentration range of 10-15 µg/mL</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Minimum inhibitory concentration ≤12 µg/mL.

*Dosages recommended are for patients with normal renal function.

†Pediatric dose should not exceed that of a normal adult.

§Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy.

¶Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.

†Pediatric dose should not exceed that of a normal adult.

§Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.

¶Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy.

†Pediatric dose should not exceed that of a normal adult.
small" number of cases; and (3) the risk of antibiotic-related adverse events exceeds the benefits of prophylactic therapy. Improving general dental hygiene was felt to be a more important factor in reducing the risk of infective endocarditis resulting from routine daily bacteremias. The current recommendations limit the use of prophylaxis to those patients with cardiac conditions associated with the greatest risk of an adverse outcome from infective endocarditis (Table 437-6). Patients with permanently damaged valves from rheumatic heart disease should also be considered for prophylaxis. Prophylaxis for these patients is recommended for "all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa." Furthermore, "placement of removable prostodontic or endodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa" are not indications for prophylaxis. Given that many invasive respiratory tract procedures do cause bacteremia, prophylaxis for many of these procedures is considered reasonable. In contrast to prior recommendations, prophylaxis for gastrointestinal or genitourinary procedures is no longer recommended in the majority of cases. Prophylaxis for patients undergoing cardiac surgery with placement of prosthetic material is still recommended. Given the highly individual nature of these recommendations and the continued concern amongst some cardiologists over their adoption, direct consultation with the child’s cardiologist is still the best method for determining a specific patient’s ongoing need for prophylaxis (Table 437-7).

Continuing education regarding both oral hygiene and, in appropriate cases, the need for prophylaxis is important, especially in teenagers.

Table 437-5  Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSAGE* AND ROUTE</th>
<th>DURATION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXACILLIN-SUSCEPTIBLE STRAINS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin or oxacillin with Optional addition of gentamicin sulfate</td>
<td>12 g/24 hr IV in 4-6 equally divided doses</td>
<td>6 wk</td>
<td>For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk</td>
</tr>
<tr>
<td>Cefazolin with Optional addition of gentamicin sulfate</td>
<td>6 g/24 hr IV in 3 equally divided doses</td>
<td>6 wk</td>
<td>Clinical benefit of aminoglycosides has not been established</td>
</tr>
<tr>
<td>For penicillin-allergic (nonanaphylactoid-type) patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin with Optional addition of gentamicin sulfate</td>
<td>3 mg/kg per 24 hr IV/IM in 2 or 3 equally divided doses</td>
<td>3-5 day</td>
<td>Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin</td>
</tr>
<tr>
<td>OXACILLIN-RESISTANT STRAINS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>30 mg/kg per 24 hr IV in 2 equally divided doses</td>
<td>6 wk</td>
<td>Adjust vancomycin dosage to achieve 1 hr serum concentration of 30-45 μg/mL and trough concentration of 10-15 μg/mL</td>
</tr>
</tbody>
</table>

IE, infective endocarditis.
*Dosages recommended are for patients with normal renal function.
†Penicillin G 24 million U/24 hr IV in 4-6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 μg/mL) and does not produce β-lactamase.
§Pediatric dose should not exceed that of a normal adult.
¶For specific dosing adjustment and issues concerning vancomycin, see Table 437-4 footnotes.

Table 437-6  2007 Statement of the American Heart Association (AHA): Cardiac Conditions Associated with the Highest Risk of an Adverse Outcome from Infective Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic cardiac valve or prosthetic material used for cardiac valve repair</td>
<td>Previous infective endocarditis</td>
</tr>
<tr>
<td>CONGENITAL HEART DISEASE (CHD)*</td>
<td></td>
</tr>
<tr>
<td>Unrepaired cyanotic CHD, including palliative shunts and conduits</td>
<td>Completely repaired CHD with prosthetic material or device, whether placed by surgery or catheter intervention, during the 1st 6 mo after the procedure</td>
</tr>
<tr>
<td>Completely repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch, or prosthetic device (which inhibit endothelialization)</td>
<td>Cardiac transplantation recipients who develop cardiac valvulopathy</td>
</tr>
</tbody>
</table>

*Except for the conditions listed here, antibiotic prophylaxis is no longer recommended by the AHA for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.
and young adults. Vigorous treatment of sepsis and local infections and careful asepsis during heart surgery and catheterization reduce the incidence of infective endocarditis.

Bibliography is available at Expert Consult.
Bibliography


Rheumatic involvement of the valves is the most important sequelae of acute rheumatic fever (see Chapter 183.1). The valvular lesions begin as small verrucae composed of fibrin and blood cells along the borders of one or more of the heart valves. The mitral valve is affected most often, followed in frequency by the aortic valve; right-sided heart manifestations are rare. As the inflammation subsides, the verrucae tend to disappear and leave scar tissue. With repeated attacks of rheumatic fever, new verrucae form near the previous ones, and the mural endocardium and chordae tendineae become involved.

A single episode of acute rheumatic fever usually results in complete healing of valvular lesions while repeated episodes, especially on previously affected valves result in rheumatic heart disease. Diagnosing acute rheumatic fever requires the fulfillment of the Jones criteria (see Chapter 183.1), while the diagnosis of rheumatic heart disease is based on cardiac auscultation signs of mitral or aortic valve involvement, which may not detect early valve injury. Screening large populations at risk for rheumatic heart disease with echocardiography has demonstrated a substantially greater number of patients with rheumatic heart disease than those detected by auscultation (Fig. 438-1). If this is confirmed, it has important public health significance in that many more patients will need to receive prophylaxis to prevent further episodes of acute rheumatic fever and worsening of valve injury.

**PATTERNS OF VALVULAR DISEASE**

**Mitral Insufficiency**

**Pathophysiology**

Mitral insufficiency is the result of structural changes that usually include some loss of valvular substance and shortening and thickening of the chordae tendineae. During acute rheumatic fever with severe cardiac involvement, heart failure is caused by a combination of mitral insufficiency coupled with inflammatory disease of the pericardium, myocardium, endocardium, and epicardium. Because of the high volume load and inflammatory process, the left ventricle becomes enlarged. The left atrium dilates as blood regurgitates into this chamber. Increased left atrial pressure results in pulmonary congestion and symptoms of left-sided heart failure. Spontaneous improvement usually occurs with time, even in patients in whom mitral insufficiency is severe at the onset. The resultant chronic lesion is most often mild or moderate in severity, and the patient is asymptomatic. More than half of patients with acute mitral insufficiency no longer have the mitral murmur 1 yr later. In patients with severe chronic mitral insufficiency, pulmonary arterial pressure becomes elevated, the right ventricle and atrium become enlarged, and right-sided heart failure subsequently develops.

**Clinical Manifestations**

The physical signs of mitral insufficiency depend on its severity. With mild disease, signs of heart failure are not present, the precordium is quiet, and auscultation reveals a high-pitched holosystolic murmur at the apex that radiates to the axilla. With severe mitral insufficiency, signs of chronic heart failure may be noted. The heart is enlarged, with a heaving apical left ventricular impulse and often an apical systolic thrill. The 2nd heart sound may be accentuated if pulmonary hypertension is present. A 3rd heart sound is generally prominent. A holosystolic murmur is heard at the apex with radiation to the axilla. A short mid-diastolic rumbling murmur is caused by increased blood flow across the mitral valve as a result of the insufficiency. Auscultation of a diastolic murmur does not necessarily mean that mitral stenosis is present. The latter lesion takes many years to develop and is characterized by a diastolic murmur of greater length, usually with presystolic accentuation.

The electrocardiogram and chest x-rays are normal if the lesion is mild. With more severe insufficiency, the electrocardiogram shows prominent bifid P waves, signs of left ventricular hypertrophy, and associated right ventricular hypertrophy if pulmonary hypertension is present. Roentgenographically, prominence of the left atrium and ventricle can be seen. Congestion of perihilar vessels, a sign of pulmonary venous hypertension, may also be evident. Calcification of the mitral valve is rare in children. Echocardiography shows enlargement of the
left atrium and ventricle, an abnormally thickened mitral valve, and Doppler studies demonstrate the severity of the mitral regurgitation. Heart catheterization and left ventriculography are considered only if diagnostic questions are not totally resolved by noninvasive assessment.

Complications

Severe mitral insufficiency may result in cardiac failure that may be precipitated by progression of the rheumatic process, the onset of atrial fibrillation, or infective endocarditis. The effects of chronic mitral insufficiency may become manifest after many years and include right ventricular failure and atrial and ventricular arrhythmias.

Treatment

In patients with mild mitral insufficiency, prophylaxis against recurrence of rheumatic fever is all that is required. Treatment of complicating heart failure (see Chapter 442), arrhythmias (see Chapter 435), and infective endocarditis (see Chapter 437) is described elsewhere. Afterload-reducing agents (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) may reduce the regurgitant volume and preserve left ventricular function. Surgical treatment is indicated for patients who despite adequate medical therapy have persistent heart failure, dyspnea with moderate activity, and progressive cardiomegaly, often with pulmonary hypertension. Although annuloplasty provides good results in some children and adolescents, valve replacement may be required. In patients with a prothetic mitral valve replacement, prophylaxis against bacterial endocarditis is warranted for dental procedures, as the routine antibiotics taken by these patients for rheumatic fever prophylaxis are insufficient to prevent endocarditis.

Mitrail Stenosis

Pathophysiology

Mitrail stenosis of rheumatic origin results from fibrosis of the mitral ring, commissural adhesions, and contracture of the valve leaflets, chordae, and papillary muscles over time. It usually takes 10 yr or more for the lesion to become fully established, although the process may occasionally be accelerated. Rheumatic mitral stenosis is seldom encountered before adolescence and is not usually recognized until adult life. Significant mitral stenosis results in increased pressure and enlargement and hypertrophy of the left atrium, pulmonary venous hypertension, increased pulmonary vascular resistance, and pulmonary hypertension. Right ventricular hypertrophy and right atrial dilatation ensue and are followed by right ventricular dilatation, tricuspid regurgitation, and clinical signs of right-sided heart failure.

Clinical Manifestations

Generally, the correlation between symptoms and the severity of obstruction is good. Patients with mild lesions are asymptomatic. More severe degrees of obstruction are associated with exercise intolerance and dyspnea. Critical lesions can result in orthopnea, paroxysmal nocturnal dyspnea, and overt pulmonary edema, as well as atrial arrhythmias. When pulmonary hypertension has developed, right ventricular diastolic dilatation may result in functional tricuspid insufficiency, hepatomegaly, ascites, and edema. Hemoptysis caused by rupture of bronchial or pleurolar veins and, occasionally, by pulmonary infarction may occur.

Jugular venous pressure is increased in severe disease with heart failure, tricuspid valve disease, or severe pulmonary hypertension. In mild disease, heart size is normal; however, moderate cardiomegaly is usual with severe mitral stenosis. Cardiac enlargement can be massive when atrial fibrillation and heart failure supervene. A parasternal right ventricular lift is palpable when pulmonary pressure is high. The principal auscultatory findings are a loud 1st heart sound, an opening snap of the mitral valve, and a long, low-pitched, rumbling mitral diastolic murmur with presystolic accentuation at the apex. The mitral diastolic murmur may be virtually absent in patients who are in significant heart failure. A holosystolic murmur secondary to tricuspid insufficiency may be audible. In the presence of pulmonary hypertension, the pulmonary component of the 2nd heart sound is accentuated. An early diastolic murmur may be caused by associated rheumatic aortic insufficiency or pulmonary valvular insufficiency secondary to pulmonary hypertension.

Electrocardiograms and roentgenograms are normal if the lesion is mild; as the severity increases, prominent and notched P waves and varying degrees of right ventricular hypertrophy become evident. Atrial fibrillation is a common late manifestation. Moderate or severe lesions are associated with roentgenographic signs of left atrial enlargement and prominence of the pulmonary artery and right-sided heart chambers; calcifications may be noted in the region of the mitral valve. Severe obstruction is associated with a redistribution of pulmonary blood flow so that the apices of the lung have greater perfusion (the reverse of normal). Echocardiography shows thickening of the mitral valve, distinct narrowing of the mitral orifice during diastole and left atrial enlargement. Doppler can estimate the transmitral pressure gradient. Cardiac catheterization quantitates the diastolic gradient across
the mitral valve, allows for the calculation of valve area, and assesses the degree of elevation of pulmonary arterial pressure.

**Treatment**

Intervention is indicated in patients with clinical signs and hemodynamic evidence of severe obstruction but before the severe manifestations outlined earlier. Surgical valvotomy or balloon catheter mitral valvuloplasty generally yields good results; valve replacement is avoided unless absolutely necessary. Balloon valvuloplasty is indicated for symptomatic, stenotic, pliable, noncalcified valves of patients without atrial arrhythmias or thrombi.

**Aortic Insufficiency**

In chronic rheumatic aortic insufficiency, sclerosis of the aortic valve results in distortion and retraction of the cusps. Regurgitation of blood leads to volume overload with dilation and hypertrophy of the left ventricle. Combined mitral and aortic insufficiency is more common than aortic involvement alone.

**Clinical Manifestations**

Symptoms are unusual except in severe aortic insufficiency. The large stroke volume and forceful left ventricular contractions may result in palpitations. Sweating and heat intolerance are related to excessive vasodilation. Dyspnea on exertion can progress to orthopnea and pulmonary edema; angina may be precipitated by heavy exercise. Nocturnal attacks with sweating, tachycardia, chest pain, and hypertension may occur.

The pulse pressure is wide with bounding peripheral pulses. Systolic blood pressure is elevated, and diastolic pressure is lowered. In severe aortic insufficiency, the heart is enlarged, with a left ventricular apical heave. A diastolic thrill may be present. The typical murmur begins immediately with the 2nd heart sound and continues until late in diastole. The murmur is heard over the upper and midleft sternal border with radiation to the apex and upper right sternal border. Characteristically, it has a high-pitched blowing quality and is easily audible in full expiration with the diaphragm of the stethoscope placed firmly on the chest and the patient leaning forward. An aortic systolic ejection murmur is frequent because of the increased stroke volume. An apical presystolic murmur (Austin Flint murmur) resembling that of mitral stenosis is sometimes heard and is a result of the large regurgitant aortic flow in diastole preventing the mitral valve from opening fully.

Chest x-rays show enlargement of the left ventricle and aorta. The electrocardiogram may be normal, but in advanced cases it reveals signs of left ventricular hypertrophy and strain with prominent P waves. The echocardiogram shows a large left ventricle and diastolic mitral valve flutter or oscillation caused by regurgitant flow hitting the valve leaflets. Doppler studies demonstrate the degree of aortic runoff into the left ventricle. Magnetic resonance angiography (MRA) can be useful in quantitating regurgitant volume. Cardiac catheterization is necessary only when the echocardiographic data are equivocal.

**Prognosis and Treatment**

Mild and moderate lesions are well tolerated. Unlike mitral insufficiency, aortic insufficiency does not regress. Patients with combined lesions during the episode of acute rheumatic fever may have only aortic involvement 1-2 yr later. Treatment consists of afterload reducers (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) and prophylaxis against recurrence of acute rheumatic fever. Surgical intervention (valve replacement) should be carried out well in advance of the onset of heart failure, pulmonary edema, or angina, when signs of decreasing myocardial performance become evident as manifested by increasing left ventricular dimensions on the echocardiogram. Surgery is considered when early symptoms are present, ST-T wave changes are seen on the electrocardiogram, or evidence of decreasing left ventricular ejection fraction is noted.

**Tricuspid Valve Disease**

Primary tricuspid involvement is rare after rheumatic fever. Tricuspid insufficiency is more common secondary to right ventricular dilation resulting from unrepaired left-sided lesions. The signs produced by tricuspid insufficiency include prominent pulsations of the jugular veins, systolic pulsations of the liver, and a blowing holosystolic murmur at the lower left sternal border that increases in intensity during inspiration. Concomitant signs of mitral or aortic valve disease, with or without atrial fibrillation, are frequent. In these cases, signs of tricuspid insufficiency decrease or disappear when heart failure produced by the left-sided lesions is successfully treated. Tricuspid valvuloplasty may be required in rare cases.

**Pulmonary Valve Disease**

Pulmonary insufficiency usually occurs on a functional basis secondary to pulmonary hypertension and is a late finding with severe mitral stenosis. The murmur (Graham Steell murmur) is similar to that of aortic insufficiency, but peripheral arterial signs (bounding pulses) are absent. The correct diagnosis is confirmed by two-dimensional echocardiography and Doppler studies.

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


The extremely heterogeneous heart muscle diseases associated with structural remodeling and/or abnormalities of cardiac function (cardiomyopathy) are important causes of morbidity and mortality in the pediatric population. Several classification schemes have been formulated in an effort to provide logical, useful, and scientifically based etiologies for the cardiomyopathies. Insight into the molecular genetic basis of cardiomyopathies has increased exponentially and etiologic classification schemes continue to evolve.

Table 439-1 classifies the cardiomyopathies based on their anatomic (ventricular morphology) and functional pathophysiology. Dilated cardiomyopathy, the most common form of cardiomyopathy, is characterized predominantly by left ventricular dilation and decreased left ventricular systolic function (Fig. 439-1). Hypertrophic cardiomyopathy demonstrates increased ventricular myocardial wall thickness, normal or increased systolic function, and often, diastolic (relaxation) abnormalities (Table 439-2; Figs. 439-2 and 439-3). Restrictive cardiomyopathy is characterized by nearly normal ventricular chamber size and wall thickness with preserved systolic function, but dramatically impaired diastolic function leading to elevated filling pressures and atrial enlargement (Fig. 439-4). Arrhythmogenic right ventricular cardiomyopathy and left ventricular noncompaction are characterized by specific morphologic abnormalities and heterogeneous functional disturbances.

Bibliography is available at Expert Consult.
Bibliography
### Table 439-1: Etiology of Pediatric Myocardial Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dilated Cardiomyopathy (DCM)</strong></td>
<td></td>
</tr>
<tr>
<td>Neuromuscular diseases</td>
<td>Muscular dystrophies (Duchenne, Becker, limb girdle, Emery-Dreifuss, congenital muscular dystrophy, etc.), myotonic muscular dystrophy, myofibrillar myopathy</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Fatty acid oxidation disorders (trifunctional protein, VLCAD), carnitine abnormalities (carnitine transport, CPTI, CPTII), mitochondrial disorders (including Kearns-Sayre syndrome), organic acidemias (propionic acidemia)</td>
</tr>
<tr>
<td>Genetic mutations in cardiomyocyte structural apparatus</td>
<td>Familial or sporadic DCM</td>
</tr>
<tr>
<td>Genetic syndromes</td>
<td>Aislm syndrome, Barth syndrome (phospholipid disorders)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>Most common in adults</td>
</tr>
<tr>
<td>Chronic tachyarrhythmias</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertrophic Cardiomyopathy (HCM)</strong></td>
<td>Mitochondrial disorders (including Friedreich ataxia, mutations in nuclear or mitochondrial genome), storage disorders (glycogen storage disorders, especially Pompe; mucopolysaccharidoses; Fabry disease; sphingolipidoses; hemochromatosis; Danon disease)</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Familial or sporadic HCM</td>
</tr>
<tr>
<td>Genetic mutations in cardiomyocyte structural apparatus</td>
<td>Noonan, Costello, cardiofaciocutaneous, Beckwith-Wiedemann syndrome</td>
</tr>
<tr>
<td>Genetic syndromes</td>
<td>Transient hypertrophy</td>
</tr>
<tr>
<td>Infant of a diabetic mother</td>
<td></td>
</tr>
<tr>
<td><strong>Restrictive Cardiomyopathy (RCM)</strong></td>
<td>Myofibrillar myopathies, Storage disorders</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>Familial or sporadic RCM</td>
</tr>
<tr>
<td><strong>Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)</strong></td>
<td>Familial or sporadic ARVC</td>
</tr>
<tr>
<td>Genetic mutations in cardiomyocyte structural apparatus</td>
<td>X-linked (Barth syndrome), autosomal dominant, autosomal recessive, mitochondrial inheritance, or sporadic LVNC</td>
</tr>
<tr>
<td>LVNC</td>
<td></td>
</tr>
<tr>
<td><strong>SECONDARY OR ACQUIRED MYOCARDIAL DISEASE</strong></td>
<td>Viral: parvovirus B19, adenovirus, coxsackievirus A and B, echovirus, rubella, varicella, influenza, mumps, Epstein-Barr virus, cytomegalovirus, measles, poliomyelitis, smallpox vaccine, hepatitis C virus, human herpesvirus 6, HIV virus, or opportunistic infections</td>
</tr>
<tr>
<td>Myocarditis (see also Table 439-3)</td>
<td>Rickettsial: psittacosis, Coxiella, Rocky Mountain spotted fever, typhus</td>
</tr>
<tr>
<td></td>
<td>Bacterial: diphtheria, mycoplasma, meningococcus, leptospirosis, Lyme disease, typhoid fever, tuberculosis, streptococcus, listeriosis</td>
</tr>
<tr>
<td></td>
<td>Parasitic: Chagas disease, toxoplasmosis, Loa loa, Toxocara canis, schistosomiasis, cysticercosis, echinococcosis, trichinosis</td>
</tr>
<tr>
<td></td>
<td>Fungal: histoplasmosis, coccidiodomycosis, actinomycosis</td>
</tr>
<tr>
<td>Systemic inflammatory disease</td>
<td>SLE, infant of mother with SLE, scleroderma, Churg-Strauss vasculitis, rheumatoid arthritis, rheumatic fever, sarcoidosis, dermatomyositis, penarteritis nodosa, hyperesinophilic syndrome (Löffler syndrome), acute eosinophilic necrotizing myocarditis, giant cell myocarditis, Kawasaki disease</td>
</tr>
<tr>
<td>Nutritional deficiency Drugs, toxins</td>
<td>Beriberi (thiamine deficiency), kwashiorkor, Keshan disease (selenium deficiency)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Kawasaki disease, medial necrosis, anomalous left coronary artery from the pulmonary artery, other congenital coronary anomalies (anomalous right coronary, coronary ostial stenosis), familial hypercholesterolemia</td>
</tr>
<tr>
<td>Hematology-oncology Endocrine-neuroendocrine</td>
<td>Anemia, sickle cell disease, leukemia</td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism, carcinoid tumor, pheochromocytoma</td>
</tr>
</tbody>
</table>

CPTI/CPTII, carnitine palmitoyltransferase 1/2; LVNC, left ventricular noncompaction; SLE, systemic lupus erythematosus; VLCAD, very long chain acyl coenzyme A dehydrogenase.
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Figure 439-1  Echocardiogram of a patient with dilated cardiomyopathy. A, Parasternal long-axis view showing the enlarged left ventricle. B, Apical 4-chamber view showing the large left ventricle compressing the right ventricle. Ao, ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

<table>
<thead>
<tr>
<th>Table 439-2</th>
<th>Cardiomyopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCM</td>
</tr>
<tr>
<td>Prevalence</td>
<td>50/100,000</td>
</tr>
<tr>
<td>Familial</td>
<td>30-50% AD, AR, X-L, Mt</td>
</tr>
</tbody>
</table>

Genes*  
Sarcomere: MYH7, MYBPC3, TNNI3, TNNT2, TNNC1, MYH6, TPM1, ACTC1  
Cytoskeleton or Z-disc: DMD, TTN, CSRP3, TCAP, VCL, ACTN2, DES, LDB3, SGCD, MYPN, ANKRD1, BAG3, NEBL, NEXN  
Nuclear envelope: LMNA, EMD, TMPO  
Cardiolipin metabolism: TAZ  
Mitochondrial function: mt DNA depletion; Mt genome mutations/deletions  
Other: CYR61, SCNSA, EYA4, ABCC9, PLN, PSEN1, PSEN2, FCMD, ALMS1, CAV3, LAMA4, LAMP2, RBBM20  

Sarcomere: MYH7, MYBPC3, MYL2, MYL3, TNNT2, TNNI3, TNNC1, MYH6, TPM1, ACTC1  
Cytoskeleton or Z-disc: TTN, CSRP3, LDB3, TCAP, VCL, ACTN2, MYOZ2, ANKRD1, BAG3  
Storage: PRKAG2, LAMP2, GLA, GAA, AGL  
Mitochondrial function: FRDA, SCO2, SURF1, COX genes, ANTI, Mt genome mutations/deletions  
Cell signaling: PTPN11, RAL1, SOS1, KRAS, HRAS, BRAF, MEK1, MEK2, MYLK2  
Other: PLN, JPH2, CALR3  

Sarcomere: MYH7, MYBPC3, ACTC1  
Cytoskeleton or Z-disc: DES  
Cardiolipin metabolism: TAZ  
Mitochondrial function: see HCM and DCM  
Other: CASQ2, DTNA  

Sudden death  
Yes  
Yes  
Yes  
Yes  
Yes  
Arrhythmias  
Atrial, ventricular, and conduction disturbances  
Atrial and ventricular fibrillation  
Ventricular and conduction disturbances  

Ventricular function  
Systolic and diastolic dysfunction  
Diastolic dysfunction  
Dynamic systolic outflow obstruction  
Diastolic dysfunction  
Normal systolic function  
Systolic or diastolic dysfunction  
Normal-reduced systolic and diastolic function  

ACE, angiotensin-converting enzyme; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVNC, left ventricular noncompaction; Mt, mitochondrial inheritance; RCM, restrictive cardiomyopathy; X-L, X-linked inheritance.

*Genes are listed using the human gene symbol.
ETIOLOGY AND EPIDEMIOLOGY

Dilated cardiomyopathy (DCM), the most common form of cardiomyopathy in children, is the cause of significant morbidity and mortality as well as a common indication for cardiac transplantation. The etiologies are diverse. Unlike adult patients with DCM, ischemic etiologies are rare in children, although these include anomalous origin of the left coronary artery from the pulmonary artery, premature coronary atherosclerosis (homozygous type II hypercholesterolemia), and coronary inflammatory diseases, such as Kawasaki disease. It is estimated that up to 50% of cases are genetic (usually autosomal dominant; some
are autosomal recessive or X-linked), including some with metabolic causes (see Table 439-1). Although the most common etiology of DCM remains idiopathic, it is likely that undiagnosed familial/genetic conditions and myocarditis predominate. Associate features may include conduction defects or sensorineural hearing loss. The annual incidence of DCM in children younger than 18 yr is 0.57 cases per 100,000 per year. Incidence is higher in males, African-Americans, and in infants less than 1 yr old.

PATHOGENESIS
The pathogenesis of the ventricular dilation and altered contractility seen in DCM varies depending on the underlying etiology; systolic dysfunction and myocardial injury are common. Genetic abnormalities of several components of the cardiac muscle including sarcomere protein, the cytoskeleton, and the proteins that bridge the contractile apparatus to the cytoskeleton, have been identified in autosomal dominant and X-linked inherited disorders. DCM can occur following viral myocarditis and, although the primary pathogenesis varies from direct myocardial injury to viral-induced inflammatory injury, the resulting myocardial damage, ventricular enlargement, and altered function likely occur by a final common pathway similar to that which occurs in genetic disorders.

In 20-50% of cases, the DCM is familial with autosomal dominant inheritance most common (see Table 439-2). Duchenne and Becker muscular dystrophies (see Chapter 609.1) are X-linked cardiomyopathies that account for 5-10% of familial DCM cases. These dystrophinopathies result in an abnormal sarcomere—cytoskeleton connection, causing impaired myocardial force generation, myocyte damage/scarring, chamber enlargement, and altered function.

Mitochondrial myopathies, like the muscular dystrophies, may present clinically with a predominance of extracardiac findings and are inherited in a recessive or mitochondrial pattern. Disorders of fatty acid oxidation present with systemic derangements of metabolism (hypoketotic hypoglycemia, acidosis, and hepatic dysfunction), some with peripheral neuropathy and neuropathy, and others with sudden death or life-threatening cardiac arrhythmias.

Anthracocine cardiotoxicity (doxorubicin [Adriamycin]) on rare occasion causes acute inflammatory myocardial injury, but more classically results in DCM and occurs in up to 30% of patients given a cumulative dose of doxorubicin exceeding 550 mg/m². The risk of toxicity appears to be exacerbated by concomitant radiation therapy.

CLINICAL MANIFESTATIONS
Although more prevalent in patients less than 1 yr of age, all age groups may be affected. Clinical manifestations of DCM are most commonly those of heart failure, but can also include palpitations, syncope, and sudden death. Irritability or lethargy can be accompanied by additional nonspecific complaints of failure to thrive, nausea, vomiting, or abdominal pain. Respiratory symptoms (tachypnea, wheezing, cough, or dyspnea on exertion) are often present. Uncommonly, patients may present acutely with pallor, altered mentation, hypotension, and shock.

Patients can be tachycardic with narrow pulse pressure and have hepatic enlargement, and rales or wheezing. The precordial cardiac impulse is increased and the heart may be enlarged to palpation or echo Doppler studies can reveal evidence of pulmonary hypertension, mitral regurgitation, or other structural cardiac or coronary abnormalities.

Additional testing should include complete blood count, renal and liver function tests, creatine phosphokinase, cardiac troponin I, lactate, brain natriuretic peptide, plasma amino acids, urine organic acids, and an acylcarnitine profile. Additional genetic and enzymatic testing may be useful (see Table 439-2). Cardiac catheterization and endomyocardial biopsy are not routine but may be useful in patients with acute DCM. Biopsy samples can be examined histologically for the presence of mononuclear cell infiltrates, myocardial damage, storage abnormalities, and for evidence of infection. It is considered standard of care to screen 1st-degree family members utilizing echocardiography and electrocardiogram (ECG) in idiopathic and familial cases of DCM.

PROGNOSIS AND MANAGEMENT
The 1 and 5 yr freedom from death or transplantation in patients diagnosed with DCM is 61% and 47%, respectively. Independent risk factors at DCM diagnosis for subsequent death or transplantation include older age, congestive heart failure, lower left ventricular fractional shortening z score, and underlying etiology. DCM is the most common cause for cardiac transplantation in pediatric and adult studies.

The therapeutic approach to patients with DCM includes a careful assessment to uncover possible treatable etiologies, screening of family members, and rigorous pharmacologic therapy. Decongestive therapy may improve symptoms of heart failure, prolong survival, and occasionally results in complete resolution of dysfunction. Patients are often treated with diuretics and angiotensin-converting enzyme inhibitors. The use of digitalis and angiotensin receptor blockers may be of additional benefit. β-Adrenergic blockade with carvedilol or metoprolol is often used in patients with chronic heart failure although pediatric specific outcome data have failed to show effectiveness. In patients presenting with extreme degrees of heart failure or circulatory collapse, intensive care measures are often required, including intravenous inotropes and diuretics, mechanic ventilatory support, and on occasion, mechanical circulatory support, which may include ventricular assist devices, extracorporeal membrane oxygenation, and ultimately cardiac transplantation. In patients with DCM and atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be instituted.

Bibliography is available at Expert Consult.

439.2 Hypertrophic Cardiomyopathy
Robert L. Spicer and Stephanie M. Ware

ETIOLOGY AND EPIDEMIOLOGY
Hypertrophic cardiomyopathy (HCM) is a heterogeneous, relatively common, and potentially life-threatening form of cardiomyopathy. The causes of HCM are heterogeneous and include inborn errors of metabolism, neuromuscular disorders, syndromic conditions, and genetic abnormalities of the structural components of the cardiomyocyte (see Table 439-1). Both the age of onset and associated features are helpful in identifying the underlying etiology.

HCM is a genetic disorder and frequently occurs as a result of mutations in sarcomere or cytoskeletal components of the cardiomyocyte (see Fig. 439-2). Mutations of the genes encoding cardiac β-myosin heavy-chain (MYH7) and myosin-binding protein C (MYBP3) are the most common (see Table 439-2). Mutations are inherited in an autosomal dominant pattern with widely variable penetrance; many cases represent de novo mutations. Some patients have mutations in more than 1 sarcomere or cytoskeletal gene and may manifest disease earlier and with more-severe symptoms. Additional genetic causes for HCM include nonsarcomeric protein mutations, such as the β-regulatory subunit of adenosine monophosphate–activated protein kinase (PRKAG2) and the lysosome-associated membrane protein 2α-galactosidase (Danon disease, a form of glycogen storage disease). Syndromic conditions, such as Noonan syndrome, may present with
Bibliography
HCM at birth and recognition of extracardiac manifestations is important in making the diagnosis. Glycogen storage disorders such as Pompe disease often present in infancy with a heart murmur, abnormal ECG, systemic signs and symptoms, and occasionally heart failure. The characteristic ECG in Pompe disease demonstrates prominent P waves, a short P-R interval, and massive QRS voltages; the echocardiogram confirms severe, often concentric, left ventricular hypertrophy.

**PATHOGENESIS**

HCM is characterized by the presence of increased left ventricular wall thickness in the absence of structural heart disease or hypertension. Often the interventricular septum is disproportionately involved, leading to the previous designation of idiopathic hypertrophic subaortic stenosis or the current term of asymmetric septal hypertrophy. In the presence of a resting or provokable outflow tract gradient, the term hypertrophic obstructive cardiomyopathy is used. Although the left ventricle is predominantly affected, the right ventricle may be involved, particularly in infancy. The mitral valve can demonstrate systolic anterior motion and mitral insufficiency. Left ventricular outflow tract obstruction occurs in 25% of patients, is dynamic in nature, and may in part be secondary to the abnormal position of the mitral valve as well as the obstructing subaortic hypertrophic cardiac muscle. The cardiac myofibrils and myofilaments demonstrate disarray and myocardial fibrosis.

Typically, systolic pump function is preserved or even hyperdynamic, though systolic dysfunction may occur late. Outflow tract obstruction with or without mitral insufficiency may be provoked by physiologic manipulations such as the Valsalva maneuver, positional changes, and physical activity. Frequently, the hypertrophic and fibrosed cardiac muscle demonstrates relaxation abnormalities (diminished compliance) and left ventricular filling may be impaired (diastolic dysfunction).

**CLINICAL MANIFESTATIONS**

Many patients are asymptomatic, and 50% of cases present with a heart murmur or during screening when another family member has been diagnosed with HCM. Symptoms of HCM may include palpitations, chest pain, easy fatigability, dyspnea, dizziness, and syncope. Sudden death is a well-recognized but uncommon manifestation that often occurs during physical exertion.

Characteristic physical examination findings include an overactive precordial impulse with a lift or heave, abnormal peripheral pulses (hyperdynamic or diminished), a systolic ejection murmur in the aortic region not associated with an ejection click, and an apical blowing murmur of mitral insufficiency.

**DIAGNOSIS**

The ECG typically demonstrates left ventricular hypertrophy with ST segment and T-wave abnormalities. Intraventricular conduction delays and signs of ventricular preexcitation (Wolf-Parkinson-White syndrome) may be present and should raise the possibility of Danon disease or Pompe disease. Chest radiography demonstrates normal or mildly increased heart size with a prominence of the left ventricle. Echocardiography is diagnostic in identifying, localizing, and quantifying the degree of myocardial hypertrophy (see Fig. 439-3). Doppler interrogation defines, localizes, and quantifies the degree of ventricular outflow tract obstruction and also demonstrates and quantifies the degree of mitral insufficiency. Diastolic dysfunction can be confirmed by M-mode, flow, and tissue Doppler techniques.

Cardiac catheterization may be indicated in some cases of HCM to define the left ventricular outflow gradient with and without pharmacologic provocation, to measure left ventricular diastolic pressures, to perform electrophysiologic testing of assessment of arrhythmia risk, or in rare cases, endomyocardial biopsy.

Additional diagnostic studies include metabolic testing, genetic testing for specific syndromes, or genetic testing for mutations in genes known to cause isolated HCM (see Table 439-2). The clinical availability of these tests is expanding. In adults, where isolated HCM is a common genetic diagnosis, it has been possible to identify a subset of mutations that confer an increased risk for arrhythmia or sudden death. As identification of the molecular basis of disease in children increases, similar correlations are expected to emerge. In addition, genetic diagnosis is useful to identify at-risk family members who require ongoing surveillance.

**PROGNOSIS AND MANAGEMENT**

Children under 1 yr of age or with inborn errors of metabolism or malformation syndromes or those with a mixed HCM/DCM have a significantly poorer prognosis. The risk of sudden death in older patients is greater in those with a history of cardiac arrest, ventricular tachycardia, exercise hypotension, syncope, excessive (>3 cm) ventricular wall thickness, and a ventricular obstruction gradient greater than 30 mm Hg. Although intrafamilial variability in symptoms occurs, a family history of sudden death is a highly significant predictor of risk.

Competitive sports and strenuous physical activity should be prohibited as most sudden deaths in patients with HCM occur during or immediately after vigorous physical exertion. β-adrenergic blocking agents (propranolol, atenolol) or calcium channel blocking agents (verapamil) may be useful in diminishing ventricular outflow tract obstruction, modifying ventricular hypertrophy, and improving ventricular filling. Although significant symptomatic improvement occurs in some patients, the risk for development of heart failure or sudden death has not been lessened. In patients with atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be used. Patients with documented ventricular arrhythmias, strong family histories of arrhythmias or sudden death, or patients with syncope should be treated with an implantable cardioverter defibrillator.

Innovative interventional procedures to anatomically or physiologically reduce the degree of left ventricular outflow tract obstruction have been used. Dual-chamber pacing, alcohol septal ablation, surgical septal myomectomy, and mitral valve replacement have all met with some success.

First-degree relatives of patients identified as having HCM should be screened with electrocardiography and echocardiography. Genetic testing is available clinically. It is important to first test the affected individual in the family rather than “at-risk” individuals because 20-40% of cases of HCM will not demonstrate mutations in currently available panels of genes. If a causative mutation is identified, “at-risk” members of the family can be effectively tested. In families with HCM without demonstrable gene mutations, repeat noninvasive cardiac screening with ECG and echo should be undertaken in at risk individuals every 3-5 yr for patients younger than 12 yr of age and yearly throughout the teenage years and young adulthood. The clinical course of other affected family members and the results of genetic testing may be of some use in stratifying risk in an affected child.

Bibliography is available at Expert Consult.

439.3 Restrictive Cardiomyopathy

Robert L. Spicer and Stephanie M. Ware

**ETIOLOGY AND EPIDEMIOLOGY**

Restrictive cardiomyopathy (RCM) accounts for <5% of cardiomyopathy cases. Incidence increases with age, and is more common in females. In equatorial Africa, RCM accounts for a large number of deaths. Infiltrative myocardial causes and storage disorders frequently result in associated left ventricular hypertrophy and may represent HCM with restrictive physiology. Noninfiltrative causes include mutations in genes encoding sarcomeric or cytoskeletal proteins. Although there has been significant success in discovering new gene mutations causing RCM, the majority of are considered idiopathic.

**PATHOGENESIS**

RCM is characterized by normal ventricular chamber dimensions, normal myocardial wall thickness, and preserved systolic function. Dramatic atrial dilation can occur as a result of the abnormal myocardial compliance and high ventricular diastolic pressure. Autosomal
Bibliography
dominant inheritance has been demonstrated for families with mutations in sarcomeric and cytoskeletal genes.

**CLINICAL MANIFESTATIONS**
Abnormal ventricular filling, sometimes referred to as *diastolic heart failure*, is manifest in the systemic venous circulation with edema, hepatomegaly, or ascites. Elevation of left-sided filling pressures result in cough, dyspnea, or pulmonary edema. With activity, patients may experience chest pain, shortness of breath, syncope/near syncope, or even sudden death. Pulmonary hypertension and pulmonary vascular disease develop and may progress rapidly. Heart murmurs are typically absent, but a gallop rhythm may be prominent. In the presence of pulmonary hypertension, an overactive right ventricular impulse and pronounced pulmonary component of the second heart sound are present.

**DIAGNOSIS**
The characteristic electrocardiographic finding of prominent P waves is usually associated with normal QRS voltages and nonspecific ST and T-wave changes. Right ventricular hypertrophy occurs in patients with pulmonary hypertension. The chest x-ray may be normal or demonstrate a prominent atrial shadow and pulmonary vascular redistribution. The echocardiogram is often diagnostic, demonstrating normal-sized ventricles with preserved systolic function and dramatic enlargement of the atria (see Fig. 439-4). Flow and tissue Doppler interrogation reveal abnormal filling parameters. Differential diagnosis from constrictive pericarditis is critical, as the latter can be treated surgically. Magnetic resonance imaging may be necessary to demonstrate the thickened or calcified pericardium often present in constrictive pericardial disease.

**PROGNOSIS AND MANAGEMENT**
Pharmacologic treatment modalities are of limited use and the prognosis of patients with RCM is generally poor with often progressive clinical deterioration. Sudden death is a significant risk, with a 2-yr survival of 50%. When signs of heart failure exist, judicious use of diuretics can result in clinical improvement. As a result of the dramatic atrial enlargement, these patients are predisposed to the development of atrial tachyarrhythmias and thromboemboli. Antiarrhythmic agents may be necessary and anticoagulation with platelet inhibitors or Coumadin is indicated.

Cardiac transplantation is the treatment of choice in many centers for patients with RCM, and the results are excellent in patients without pulmonary hypertension, pulmonary vascular disease, or severe congestive heart failure.

*Bibliography is available at Expert Consult.*

**439.4 Left Ventricular Noncompaction, Arrhythmogenic Right Ventricular Cardiomyopathy, and Endocardial Fibroelastosis**

*Robert L. Spicer and Stephanie M. Ware*

Left ventricular noncompaction (LVNC) was initially believed to be a rare disorder found only in children, but is now known to affect individuals of all ages. LVNC is characterized by a distinctive trabeculated or spongy-appearing left ventricle (Fig. 439-5) commonly associated with left ventricular hypertrophy and/or dilation, and at times, systolic or diastolic dysfunction. LVNC may be isolated or associated with structural congenital cardiac defects. Patients may present with signs of heart failure, arrhythmias, syncope, sudden death, or as an asymptomatic finding during screening of family members.

Imaging studies using ultrasound or magnetic resonance can demonstrate the characteristic pattern of deeply trabeculated left ventricle myocardium, most characteristically in the apex of the left ventricle. ECG findings are nonspecific and include chamber hypertrophy, ST and T-wave changes, or arrhythmias. In some patients, preexcitation is notable and giant QRS voltages occur in approximately 30% of younger children. Metabolic screening should be considered, especially in young children. Elevated serum lactate and urine 3-methylglutaconic acid may be seen in Barth syndrome, an X-linked disorder of phospholipid metabolism caused by a mutation in the tafazzin (TAZ) gene. Clinical testing for TAZ mutations is available and should be considered, especially in males. Patients with mitochondrial disorders frequently demonstrate signs of LVNC. These children are at risk for atrial or ventricular arrhythmias and thromboembolic complications. Treatment includes antiarrhythmics, antiarrhythmic therapy if needed, and treatment of heart failure if present. In patients refractory to medical therapy, cardiac transplantation has been used successfully.

**Arrhythmogenic right ventricular cardiomyopathy (ARVC)** is thought to be uncommon in North America but is among the most common forms of cardiomyopathy in Europe, especially Italy. Autosomal dominant inheritance is common. In addition, recessive forms associated with severe ARVC and skin manifestations are known. Comprehensive genetic screening has been reported to identify a cause in up to 50% of cases. ARVC is typically characterized by a dilated right ventricle with fibrofatty infiltration of the right ventricle wall; increasing, left ventricle involvement is being recognized. Global and regional right and left ventricular dysfunction and ventricular tachyarrhythmias are the major clinical findings. Syncope or aborted sudden death can occur and should be treated with antiarrhythmic medications and placement of a defibrillator. In patients with ventricular dysfunction, heart failure management as indicated for patients with DCM may be of use.

**Endocardial fibroelastosis (EFE),** at one time an important cause of heart failure in children, is uncommon. The decline in primary EFE is likely related to the abolition of mumps virus infections by immunization practices. Rare familial cases exist, but the causative genes are unknown. Secondary EFE can occur with severe left-sided obstructive lesions such as aortic stenosis or atresia, hypoplastic left heart syndrome, or coarctation of the aorta. EFE is characterized by an opaque, white, fibroelastic thickening on the endocardial surface of the ventricle, which leads to systolic and/or diastolic dysfunction. Surgical removal of the endocardial fibrosis has been successfully utilized to improve cardiac function. Standard heart failure management including transplantation has been utilized in the management of EFE.

*Bibliography is available at Expert Consult.*

**439.5 Myocarditis**

*Robert L. Spicer and Stephanie M. Ware*

Acute or chronic inflammation of the myocardium is characterized by inflammatory cell infiltrates, myocyte necrosis, or myocyte...
Bibliography


Bibliography


Causes of Myocarditis

<table>
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<tr>
<th>INFECTIOUS</th>
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degeneration and may be caused by infectious, connective tissue, granulomatous, toxic, or idiopathic processes. There may be associated systemic manifestations of the disease and on occasion the endocardium or pericardium is involved, though coronary pathology is uniformly absent. Patients may be asymptomatic, have nonspecific prodromal symptoms, or present with overt congestive heart failure, compromising arrhythmias, or sudden death. It is thought that viral infections are the most common etiology though myocardial toxins, drug exposures, hypersensitivity reactions, and immune disorders may also lead to myocarditis (Table 439-3).

ETIOLOGY AND EPIDEMIOLOGY

Viral Infections
Coxsackievirus and other enteroviruses, adenovirus, parvovirus, Epstein-Barr virus, parechovirus, influenza virus, and cytomegalovirus are the most common causative agents in children, though most known viral agents have been reported. In Asia, hepatitis C virus appears to be significant as well. The true incidence of viral myocarditis is unknown as mild cases probably go undetected. The disease is typically sporadic but may be epidemic. Manifestations are, to some degree, age dependent: in neonates and young infants, viral myocarditis can be fulminant; in children, it often will occur as an acute, myopericarditis with heart failure; and in older children and adolescents, it may present with signs and symptoms of acute or chronic heart failure or chest pain.

Bacterial Infections
Bacterial myocarditis has become far less common with the advent of advanced public health measures, which have minimized infectious causes such as diphtheria. Diphtheritic myocarditis (see Chapter 187) is unique as bacterial toxin may produce circulatory collapse and toxic myocarditis characterized by atroventricular block, bundle-branch block, or ventricular ectopy. Any overwhelming systemic bacterial infection can manifest with circulatory collapse and shock with evidence of myocardial dysfunction characterized by tachycardia, gallop rhythm, and low cardiac output. Additional nonviral infectious causes of myocarditis include rickettsia, protozoa, parasitic infections, and fungal disease.

PATHOPHYSIOLOGY
Myocarditis is characterized by myocardial inflammation, injury or necrosis, and ultimately fibrosis. Cardiac enlargement and diminished systolic function occur as a direct result of the myocardial damage. Typical signs of congestive heart failure occur and may progress rapidly to shock, atrial or ventricular arrhythmias, and sudden death. Viral myocarditis may also become a chronic process with persistence of viral nucleic acid in the myocardium, and the perpetuation of chronic inflammation secondary to altered host immune response including activated T lymphocytes (cytotoxic and natural killer cells) and antibody-dependent cell mediated damage. Additionally, persistent viral infection may alter the expression of major histocompatibility complex antigens with resultant exposure of neoantigens to the immune system. Some viral proteins share antigenic epitopes with host cells, resulting in autoimmune damage to the antigenically related myocyte. Cytokines such as tumor necrosis factor-α and interleukin-1 are inhibitors of myocyte response to adrenergic stimuli and result in diminished cardiac function. The final result of viral-associated inflammation can be DCM.

CLINICAL MANIFESTATIONS
Manifestations of myocarditis range from asymptomatic or nonspecific generalized illness to acute cardiogenic shock and sudden death. Infants and young children more often have a fulminant presentation with fever, respiratory distress, tachycardia, hypotension, gallop rhythm, and cardiac murmur. Associated findings may include a rash or evidence of end organ involvement such as hepatitis or aseptic meningitis.

Patients with acute or chronic myocarditis may present with chest discomfort, fever, palpitations, easy fatigability, or syncope/near syncope. Cardiac findings include overactive precordial impulse, gallop rhythm, and an apical systolic murmur of mitral insufficiency.
In patients with associated pericardial disease, a rub may be noted. Hepatic enlargement, peripheral edema, and pulmonary findings such as wheezes or rales may be present in patients with decompensated heart failure.

**DIAGNOSIS**

Electrocardiographic changes are nonspecific and may include sinus tachycardia, atrial or ventricular arrhythmias, heart block, diminished QRS voltages, and nonspecific ST and T-wave changes, often suggestive of acute ischemia. Chest x-rays in severe, symptomatic cases reveal cardiomegaly, pulmonary vascular prominence, overt pulmonary edema, or pleural effusions. Echocardiography often shows diminished ventricular systolic function, cardiac chamber enlargement, mitral insufficiency, and occasionally, evidence of pericardial infusion.

**Cardiac MRI** is a standard imaging modality for the diagnosis of myocarditis; information on the presence and extent of edema, gadolinium-enhanced hyperemic capillary leak, myocyte necrosis, left ventricular dysfunction, and evidence of an associated pericardial effusion assist in the cardiac MRI diagnosis of myocarditis.

Endomyocardial biopsy may be useful in identifying inflammatory cell infiltrates or myocyte damage and performing molecular viral analysis using polymerase chain reaction techniques. Catheterization and biopsy, although not without risk (perforation and arrhythmias), should be performed by experienced personnel in patients suspected to have myocarditis or if there is strong suspicion for unusual forms of cardiomyopathy such as storage diseases or mitochondrial defects. Nonspecific tests include sedimentation rate, creatine phosphokinase isoenzymes, cardiac troponin I, and brain natriuretic peptide levels.

**DIFFERENTIAL DIAGNOSIS**

The predominant diseases mimicking acute myocarditis include carnitine deficiency, other metabolic disorders of energy generation, hereditary mitochondrial defects, idiopathic DCM, pericarditis, EFE, and anomalies of the coronary arteries (see Table 439-1).

**TREATMENT**

Primary therapy for acute myocarditis is supportive (see Chapter 442). Acutely, the use of inotropic agents, preferably milrinone, should be entertained but used with caution because of their proarrhythmic potential. Diuretics are often required as well. If in extremis, mechanical ventilatory support and mechanical circulatory support with ventricular assist device implantation or extracorporeal membrane oxygenation may be needed to stabilize the patient's hemodynamic status and serve as a bridge to recovery or cardiac transplantation. Diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are of use in patients with compensated congestive heart failure in the outpatient setting but may be contraindicated in those presenting with fulminant heart failure and cardiovascular collapse. In patients manifesting with significant atrial or ventricular arrhythmias, specific antiarrhythmic agents (for example, amiodarone) should be administered and implantable cardioverter defibrillator placement considered.

Immunomodulation of patients with myocarditis is controversial. **Intravenous immune globulin** may have a role in the treatment of acute or fulminant myocarditis and **corticosteroids** have been reported to improve cardiac function, but the data are not convincing in children. Relapse has been noted in patients receiving immunosuppression who have been weaned from support. There are no studies to recommend specific antiviral therapies for myocarditis.

**PROGNOSIS**

The prognosis of symptomatic acute myocarditis in newborns is poor, and a 75% mortality has been reported. The prognosis is better for children and adolescents, although patients who have persistent evidence of DCM often progress to need for cardiac transplantation. Recovery of ventricular function has been reported in 10-50% of patients, however.

*Bibliography is available at Expert Consult.*
Bibliography
The heart is enveloped in a bilayer membrane, the pericardium, which normally contains a small amount of serous fluid. The pericardium is not vital to normal function of the heart, and primary diseases of the pericardium are uncommon. However, the pericardium may be affected by a variety of conditions (Table 440-1), often as a manifestation of a systemic illness and can result in serious, even life-threatening, cardiac compromise.

### 440.1 Acute Pericarditis

**Robert L. Spicer and Stephanie M. Ware**

**PATHOGENESIS**

Inflammation of the pericardium may have only minor pathophysiologic consequences in the absence of significant fluid accumulation in the pericardial space. When the amount of fluid in the nondistensible pericardial space becomes excessive, pressure within the pericardium increases and is transmitted to the heart resulting in impaired filling. Although small to moderate amounts of pericardial effusion can be well tolerated and clinically silent, once the noncompliant pericardium has been distended maximally, any further fluid accumulation causes abrupt impairment of cardiac filling and is termed cardiac tamponade. When untreated, tamponade can lead to shock and death. Pericardial effusions may be serous/transudative, exudative/purulent, fibrinous, or hemorrhagic.

<table>
<thead>
<tr>
<th><strong>Table 440-1</strong></th>
<th><strong>Etiology of Pericardial Disease</strong></th>
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<td><strong>CONGENITAL</strong></td>
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<td>Mullibrey nanism (TRIM 37 gene mutation)</td>
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<td>Camptodactyly-arthropathy-coxa vara-pericarditis syndrome (PRG4 gene mutation)</td>
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<td>Bacterial (Haemophilus influenzae, streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma, tularemia, listeria, leptospirosis, tuberculosis, Q-fever, salmonella)</td>
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<td>Metabolic (uremia, hypothyroidism, Gaucher disease, very-long-chain acyl-CoA dehydrogenase deficiency)</td>
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<td>Traumatic (surgical, catheter, blunt)</td>
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<td>Lymphomas, leukemia, radiation therapy</td>
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<td></td>
<td>Primary pericardial tumors</td>
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CLINICAL MANIFESTATIONS
The most common symptom of acute pericarditis is chest pain, typically described as sharp/stabbing, positional, radiating, worse with inspiration, and relieved by sitting upright or prone. Cough, fever, dyspnea, abdominal pain, and vomiting are nonspecific symptoms associated with pericarditis. Additionally, signs and symptoms of organ system involvement may occur in the presence of generalized systemic disease.

Muffled or distant heart sounds, tachycardia, narrow pulse pressure, jugular venous distention, and a pericardial friction rub provide clues to the diagnosis of acute pericarditis. Cardiac tamponade is recognized by the excessive fall of systolic blood pressure (>10 mm Hg) with inspiration. This pulsus paradoxus can be assessed by careful auscultatory blood pressure determination (automated blood pressure cuffs are inadequate), arterial pressure line wave form, or pulse oximeter tracing inspection. Conditions other than cardiac tamponade, which may result in pulsus paradoxus include severe dyspnea, obesity, and positive pressure ventilator support.

DIAGNOSIS
The electrocardiogram is often abnormal in acute pericarditis although the findings are nonspecific. Low voltage QRS amplitude may be seen as a result of pericardial fluid accumulation. Tachycardia and abnormalities of the ST segments, PR segments, and T waves may be present as well.

Although the chest x-ray findings in a patient with pericarditis without effusion are usually normal, in the presence of a significant effusion, cardiac enlargement will be seen and cardiac contour may be unusual (Erlenmeyer flask or water bottle appearance) (Fig. 440-1). Echocardiography is the most sensitive technique for identifying the size and location of a pericardial effusion. Compression and collapse of the right atrium and/or right ventricle are present with cardiac tamponade (Fig. 440-2). Abnormal diastolic filling parameters have also been described in cases of tamponade.

DIFFERENTIAL DIAGNOSIS
Chest pain similar to that present in pericarditis can occur with lung diseases, especially pleuritis, and with gastroesophageal reflux. Pain related to myocardial ischemia is usually more severe, more prolonged, and occurs with exercise, allowing distinction from pericarditis-induced pain. The presence of a pericardial effusion by echocardiography is virtually diagnostic of pericarditis.

Infectious Pericarditis
A number of viral agents are known to cause pericarditis, and the clinical course of the majority of these infections is mild and spontaneously resolving. The term acute benign pericarditis is synonymous for viral pericarditis. Agents identified as causing pericarditis include the enteroviruses, influenza, adenovirus, respiratory syncytial virus, and parvovirus. As the course of this illness is usually benign, symptomatic treatment with nonsteroidal antiinflammatory agents is often sufficient. Patients with large effusions and tamponade may require pericardiocentesis. Presumed viral but often idiopathic pericarditis may have an autoimmune component. In up to 30%, there may be recurrences of pericarditis. Treatment and/or prevention of recurrences with colchicine improve symptoms and avoid recurrences in most of these patients. Patients with idiopathic recurrent pericarditis may also respond to treatment with anakinra. If the condition becomes chronic or relapsing, surgical pericardiectomy or creation of a pericardial window may be necessary.

Echocardiography is useful in differentiating pericarditis from myocarditis, the latter of which will show evidence of diminished myocardial contractility or valvular dysfunction. Pericarditis and myocarditis may occur together in some cases of viral infection.

Purulent pericarditis, often caused by bacterial infections, has become much less common with the advent of new immunizations for haemophilus and pneumococcal disease. Historically, purulent pericarditis was seen in association with severe pneumonias, epiglottitis, meningitis, or osteomyelitis. Patients with purulent pericarditis are acutely ill. Unless the infection is recognized and treated expeditiously, the course can be fulminant, leading to tamponade and death. Tuberculous pericarditis is rare in developed countries, but can be seen as a relatively common complication of HIV infection in regions where tuberculosis is endemic and access to antiretroviral therapy is limited. Immune-complex mediated pericarditis is a rare complication that may result in a nonpurulent (sterile) effusion following systemic bacterial infections such as meningococcus or haemophilus.

Noninfectious Pericarditis
Systemic inflammatory diseases including autoimmune, rheumatologic, and connective tissue disorders may involve the pericardium and result in serous pericardial effusions. Pericardial inflammation may be a component of the type II hypersensitivity reaction seen in patients with acute rheumatic fever. It is often associated with rheumatic valvulitis and responds quickly to antiinflammatory agents including steroids. Tamponade is very uncommon (see Chapters 183.1 and 438).

Juvenile idiopathic arthritis, usually systemic onset disease, can manifest with pericarditis. Differentiating rheumatoid pericardial inflammation from that seen with systemic lupus erythematous is difficult and requires careful rheumatologic evaluation. Aspirin and/or corticosteroids can result in rapid resolution of a pericardial effusion but may be needed on a chronic basis to prevent relapse. Many of the autoimmune inflammatory recurrent fever syndromes present with pericarditis, usually with other manifestations of those disorders (Chapter 163).

Patients with chronic renal failure or hypothyroidism may have pericardial effusions and should be carefully screened with physical exam, and, if indicated, imaging studies, during the course of their illness should clinical suspicion arise. Especially common in referral centers with hematology/oncology units is the presence of pericardial effusion related to neoplastic disease. Conditions resulting in effusion include Hodgkin disease, lymphomas, and leukemia. Radiation therapy directed to the mediastinum of patients with malignancy can result in pericarditis and later constrictive pericardial disease.

The postpericardiotomy syndrome occurs in patients having undergone cardiac surgery and is characterized by fever, lethargy, anorexia, irritability, and chest/abdominal discomfort beginning 7-14 days postoperatively. There can be associated pleural effusions and serologic evidence of elevated antineut antibodies. Postpericardiotomy syndrome is effectively treated with aspirin, nonsteroidal inflammatory...
agents, and in severe cases, corticosteroids. Pericardial drainage is necessary in those patients with cardiac tamponade.

440.2 Constrictive Pericarditis

Robert L. Spicer and Stephanie M. Ware

Rarely, chronic pericardial inflammation can result in fibrosis, calcification, and thickening of the pericardium. Pericardial scarring may lead to impaired cardiac distensibility and filling and is termed constrictive pericarditis. Constrictive pericarditis can occur following recurrent or chronic pericarditis, cardiac surgery, or radiation to the mediastinum as a treatment for malignancies, most commonly Hodgkin disease or lymphoma.

Clinical manifestations of systemic venous hypertension predominate in cases of restrictive pericarditis. Jugular venous distention, peripheral edema, hepatomegaly, and ascites may precede signs of more significant cardiac compromise such as tachycardia, hypotension, and pulsus paradoxus. A pericardial knock, rub, and distant heart sounds might be present on auscultation. Abnormalities of liver function tests, hypoalbuminemia, hypoprothrombinemia, and lymphopenia may be present. On occasion, x-rays of the chest demonstrate calcifications of the pericardium.

Constrictive pericarditis may be difficult to distinguish clinically from restrictive cardiomyopathy as both conditions result in impaired myocardial filling (see Chapter 439.3). Echocardiography may be helpful in distinguishing constrictive pericardial disease from restrictive cardiomyopathy, but magnetic resonance imaging and computed tomographic imaging are more sensitive in detecting abnormalities of the pericardium. In rare instances, exploratory thoracotomy with direct examination of the pericardium may be required to confirm the diagnosis.

Although acute pericardial constriction is reported to respond to antiinflammatory agents, the more typical chronic constrictive pericarditis will respond only to surgical pericardiectomy with extensive resection of the pericardium.

Bibliography is available at Expert Consult.
Chapter 440  •  Diseases of the Pericardium  2281.e1

Bibliography


Although cardiac tumors occur rarely in pediatric patients, they may result in serious hemodynamic or electrophysiologic abnormalities depending on tumor type and location.

The vast majority of tumors originating from the heart are benign. Rhabdomyomas are the most common pediatric cardiac tumors and are associated with tuberous sclerosis in 70-95% of cases (see Chapter 596.2). Rhabdomyomas may occur at any age, from fetal life through late adolescence. They are often multiple, can occur in any cardiac chamber, and originate within the myocardium extending, often, into the atrial or ventricular cavities (Fig. 441-1). Depending on their location and size, they can result in inflow or outflow obstruction leading to cyanosis or cardiac failure; many are asymptomatic. Atrial and ventricular arrhythmias have been reported with rhabdomyomas, and on occasion, ventricular preexcitation (Wolff-Parkinson-White) is present on electrocardiogram.
malignant cardiac tumors. In pediatric patients, Wilms tumor and lymphoma/leukemia are the most common causes of such secondary tumors.

Although the manifestations of cardiac tumors in pediatric patients are protean, when a tumor is suspected, noninvasive imaging with echocardiography and/or magnetic resonance imaging may be diagnostic and can determine tumor type, location, extent, and hemodynamic impact. Electrocardiogram and Holter studies are valuable adjuncts when rhythm abnormalities are suspected. Cardiac catheterization is rarely indicated, but may be utilized to confirm tumor location, assess intracardiac hemodynamics, and perform biopsy for histologic assessment. Risks including blood loss, perforation, arrhythmia, and vessel injury should be considered when discussing catheterization and biopsy.

Because the natural history of rhabdomyomas is one of spontaneous diminution or complete resolution, treatment of the majority of cardiac tumors in pediatric patients is usually unnecessary. Everolimus, an inhibitor of the mammalian target of rapamycin, may enhance resolution in symptomatic patients with cardiac rhabdomyomas. Careful clinical follow-up and imaging are important. Antiarrhythmic medications may be prescribed to control rhythm disorders. Surgical removal of a cardiac tumor may be indicated to relieve obstruction, improve myocardial or valve function, or control arrhythmias. Heart transplantation has been performed in cases of unresectable tumors with significant hemodynamic compromise. Wilms tumors extending from the inferior vena cava into the atrium may require cardiopulmonary bypass support during the course of primary resection of the renal tumor. Radiation or chemotherapy can improve cardiac function in rare cases of lymphoma or leukemia compressing the heart with hemodynamic compromise.

Bibliography is available at Expert Consult.

Fibromas are the second most common pediatric cardiac tumor, and in contrast to rhabdomyomas, are usually solitary and intramyocardial. They can, by size and location, lead to heart failure, cyanosis, or rhythm disturbances. Loss of the tumor suppressor PTCH1 is associated with the development of cardiac fibromas in sporadic cases. There is an increased incidence in patients with Gorlin syndrome (3%).

Myxomas, the most common cardiac tumor seen in adults, are infrequent in the pediatric population. Myxomas are predominantly intraatrial, appear pedunculated, and are rather mobile. They may cause obstruction to inflow or outflow and may present with a murmur, heart failure, or syncope. On occasion, atrial myxomas are associated with systemic symptoms of fever, malaise, and arthralgia. Carney complex is a familial autosomal dominant multiple neoplasia (often endocrine: pituitary adenoma, thyroid, testis, ovarian) and lentiginosis syndrome in which cardiac myxomas can occur at a young age in any or all cardiac chambers. PRKAR1A is the gene mutation in some families.

Other benign tumors include hemangiomas, Purkinje cell tumors, papillomas, lipomas, and mesotheliomas. Depending on their location, these benign tumors can result in valvular function abnormalities, myocardial dysfunction, or heart block and other arrhythmias.

Malignant pediatric cardiac tumors are far less common than benign tumors (75% vs. 25%), and the vast majority of such malignancies are sarcomas including angiosarcomas, rhabdosarcomas, or fibrosarcomas. Lymphomas and phaeochromocytomas are reported but rare. Tumors originating from noncardiac sources that invade, extend, or metastasize to the heart are more commonly seen than primary
Bibliography


Heart failure occurs when the heart cannot deliver adequate cardiac output to meet the metabolic needs of the body. In the early stages of heart failure, various compensatory mechanisms are evoked to maintain normal metabolic function. When these mechanisms become ineffective, increasingly severe clinical manifestations result (see Chapter 70).

**PATHOPHYSIOLOGY**

The heart can be viewed as a pump with an output proportional to its filling volume and inversely proportional to the resistance against which it pumps. As ventricular end-diastolic volume increases, a healthy heart increases cardiac output until a maximum is reached and cardiac output can no longer be augmented (the Frank-Starling principle; Fig. 442-1). The increased stroke volume obtained in this manner is a result of stretching of myocardial fibers, but it also results in increased wall tension, which elevates myocardial oxygen consumption. Hearts working under various types of stress function along different Frank-Starling curves. Cardiac muscle with compromised intrinsic contractility requires a greater degree of dilation to produce increased stroke volume and does not achieve the same maximal
beneficial effects of sympathetic stimulation include an increase in secretion of circulating epinephrine by the adrenals and increased cardiac output is an increase in sympathetic tone secondary to increased pathoadrenal axis. One of the principal mechanisms for increasing by neurohormones such as the renin–angiotensin system and the sym

In children, the signs and symptoms of heart failure may be similar to those in adults and include fatigue, effort intolerance, anorexia, dyspnea, and cough. Many children, however, especially adolescents, may have primarily abdominal symptoms (abdominal pain, nausea, anorexia) and a surprising lack of respiratory complaints. Attention to the cardiovascular system may come only after an abdominal roentgenogram unexpectedly catches the lower end of an enlarged heart. The elevation in systemic venous pressure may be gauged by clinical assessment of jugular venous pressure and liver enlargement. Orthopnea and basal rales are variably present; edema is usually discernible in dependent portions of the body, or anasarca may be present. Cardiomegaly is invariably noted. A gallop rhythm is common; when ventricular dilation is advanced, the holosystolic murmur of mitral or tricuspid valve regurgitation may be heard.

In infants, heart failure may be difficult to distinguish from other causes of respiratory distress. Prominent manifestations include tachypnea, feeding difficulties, poor weight gain, excessive perspiration, irritability, weak cry, and noisy, labored respirations with intercostal and subcostal retractions, as well as flaring of the alae nasi. The signs of cardiac-induced pulmonary congestion may be indistinguishable from those of bronchiolitis; wheezing is often a more prominent finding in young infants with heart failure than rales. Pneumonitis with or without atelectasis is common, especially in the right middle and lower lobes, a result of bronchial compression by the enlarged heart. Hepatomegaly usually occurs, and cardiomegaly is invariably present. In spite of pronounced tachycardia, a gallop rhythm can frequently be recognized. The other auscultatory signs are those produced by the underlying cardiac lesion. Clinical assessment of jugular venous pressure in infants may be difficult because of the shortness of the neck and the difficulty of observing a relaxed state; palpation of an enlarged

**Figure 442-1 The Frank-Starling relationship.** As left ventricular end-diastolic pressure increases, the cardiac index increases, even in the presence of congestive heart failure, until a critical level of LVED pressure is reached. Adding an inotropic agent (digoxin) shifts the curve from I to II. (From Gersony WM, Steep CN. In Dickerman JD, Lucey JP, editors: Smith’s The critically ill child: diagnosis and medical management, ed 3, Philadelphia, 1984, WB Saunders.)

Cardiac output as normal myocardium does. If a cardiac chamber is already dilated because of a lesion causing increased preload (e.g., a left-to-right shunt or valvular insufficiency), there is little room for further dilation as a means of augmenting cardiac output. The presence of lesions that result in increased afterload to the ventricle (aortic or pulmonic stenosis, coartation of the aorta) decreases cardiac performance, thereby resulting in a depressed Frank-Starling relationship.

**Systemic oxygen transport** is calculated as the product of cardiac output and systemic oxygen content. **Cardiac output** can be calculated as the product of heart rate and stroke volume. The primary determinants of stroke volume are the afterload (pressure work), preload (volume work), and contractility (intrinsic myocardial function). Abnormalities in heart rate can also compromise cardiac output; for example, tachyarrhythmias shorten the diastolic time interval for ventricular filling. Alterations in the oxygen-carrying capacity of blood (e.g., anemia or hypoxemia) also lead to a decrease in systemic oxygen transport and, if compensatory mechanisms are inadequate, can result in decreased delivery of substrate to tissues.

In some cases of heart failure, cardiac output is normal or increased, yet because of decreased systemic oxygen content (secondary to anemia) or increased oxygen demands (secondary to hyperventilation, hyperthyroidism, or hypermetabolism), an inadequate amount of oxygen is delivered to meet the body’s needs. This condition, high-output failure, results in the development of signs and symptoms of heart failure when there is no basic abnormality in myocardial function and cardiac output is greater than normal. It is also seen with large systemic arteriovenous fistulas. These conditions reduce peripheral vascular resistance and cardiac afterload and increase myocardial contractility. Heart “failure” results when the demand for cardiac output exceeds the ability of the heart to respond. Chronic severe high-output failure may eventually result in a decrease in myocardial performance as the metabolic requirements of the myocardium are not met.

There are multiple systemic compensatory mechanisms used by the body to adapt to chronic heart failure. Some are mediated at the molecular/cellular level, such as upregulation or downregulation of various metabolic pathway components leading to changes in efficiency of oxygen and other substrate utilization. Others are mediated by neurohormones such as the renin–angiotensin system and the sympathetic-adrenal axis. One of the principal mechanisms for increasing cardiac output is an increase in sympathetic tone secondary to increased secretion of circulating epinephrine by the adrenals and increased release of norepinephrine at the neuromuscular junction. The initial beneficial effects of sympathetic stimulation include an increase in

**CLINICAL MANIFESTATIONS**

The clinical manifestations of heart failure depend in part on the degree of the child’s cardiac reserve. A critically ill infant or child who has exhausted the compensatory mechanisms to the point that cardiac output is no longer sufficient to meet the basal metabolic needs of the body will be symptomatic at rest. Other patients may be comfortable when quiet but are incapable of increasing cardiac output in response to even mild activity without experiencing significant symptoms. Conversely, it may take rather vigorous exercise to compromise cardiac function in children who have less severe heart disease. A thorough history is extremely important in making the diagnosis of heart failure and in evaluating the possible causes. Parents who observe their child on a daily basis may not recognize subtle changes that have occurred over the course of days or weeks. Gradually worsening perfusion or increasing respiratory effort may not be recognized as an abnormal finding. Edema may be passed off as normal weight gain, and exercise intolerance as lack of interest in an activity. The history of a young infant should also focus on feeding (see Chapter 416). An infant with heart failure often takes less volume per feeding, becomes dyspneic while sucking, and may perspire profusely. Eliciting a history of fatigue in an older child requires detailed questions about activity level and its course over several months.

In children, the signs and symptoms of heart failure may be similar to those in adults and include fatigue, effort intolerance, anorexia, dyspnea, and cough. Many children, however, especially adolescents, may have primarily abdominal symptoms (abdominal pain, nausea, anorexia) and a surprising lack of respiratory complaints. Attention to the cardiovascular system may come only after an abdominal roentgenogram unexpectedly catches the lower end of an enlarged heart. The elevation in systemic venous pressure may be gauged by clinical assessment of jugular venous pressure and liver enlargement. Orthopnea and basal rales are variably present; edema is usually discernible in dependent portions of the body, or anasarca may be present. Cardiomegaly is invariably noted. A gallop rhythm is common; when ventricular dilation is advanced, the holosystolic murmur of mitral or tricuspid valve regurgitation may be heard.

In infants, heart failure may be difficult to distinguish from other causes of respiratory distress. Prominent manifestations include tachypnea, feeding difficulties, poor weight gain, excessive perspiration, irritability, weak cry, and noisy, labored respirations with intercostal and subcostal retractions, as well as flaring of the alae nasi. The signs of cardiac-induced pulmonary congestion may be indistinguishable from those of bronchiolitis; wheezing is often a more prominent finding in young infants with heart failure than rales. Pneumonitis with or without atelectasis is common, especially in the right middle and lower lobes, a result of bronchial compression by the enlarged heart. Hepatomegaly usually occurs, and cardiomegaly is invariably present. In spite of pronounced tachycardia, a gallop rhythm can frequently be recognized. The other auscultatory signs are those produced by the underlying cardiac lesion. Clinical assessment of jugular venous pressure in infants may be difficult because of the shortness of the neck and the difficulty of observing a relaxed state; palpation of an enlarged
The abnormalities may also suggest myocardial inflammatory disease, but low-voltage QRS morphologic characteristics with ST-T-wave may correlate with other noninvasive parameters of ventricular function in assessing the cause of heart failure but does not establish the diagnosis. A chest roentgenogram performed to evaluate for a possible pulmonary infection, enlargement is often noted as an unexpected finding on a chest roentgenogram. Fluffy perihilar pulmonary markings suggestive of venous congestion and acute pulmonary edema result in flattening of the interventricular septum. Electrocardiography is the standard technique for assessing ventricular function. The most commonly used parameter in children is fractional shortening (a single dimensional variable), determined as the difference between end-systolic and end-diastolic diameter divided by end-diastolic diameter. Normal fractional shortening is between approximately 28% and 42%. In adults, the most commonly used parameter is ejection fraction (which uses 2-dimensional data to calculate a 3-dimensional volume) and the normal range is 55-65%. In children with right ventricular enlargement or other cardiac pathology resulting in flattening of the interventricular septum, ejection fraction is used because fractional shortening measured in the standard echocardiographic short-axis view will not be accurate. Doppler studies can also be used to estimate cardiac output. Doppler assessment of transmural flow can also be used as a noninvasive assessment of diastolic function. Doppler tissue imaging can assess not only cardiac function, but wall motion abnormalities that can interfere with normal synchronous cardiac contraction. Magnetic resonance angiography is also very useful in quantifying left and right ventricular function, volume and mass as well as coronary artery anatomy. If valvar regurgitation is present, magnetic resonance angiography can quantify the regurgitant fraction.

Arterial oxygen levels may be decreased when ventilation–perfusion inequalities occurs secondary to pulmonary edema. When heart failure is severe, respiratory or metabolic acidosis, or both, may be present. Infants with heart failure often display hypotension as a result of renal water retention. Chronic diuretic treatment can decrease serum sodium levels further. Serum B-type natriuretic peptide, a cardiac neurohormone released in response to increased ventricular wall tension, is elevated in adult patients with congestive heart failure. In children, B-type natriuretic peptide may be elevated in patients with heart failure as a result of systolic dysfunction (cardiomyopathy), as well as in children with volume overload (left-to-right shunts such as ventricular septal defect).

**DIAGNOSIS**

X-rays of the chest show cardiac enlargement. Pulmonary vascularity is variable and depends on the cause of the heart failure. Infants and children with large left-to-right shunts have exaggeration of the pulmonary arterial vessels to the periphery of the lung fields, whereas patients with cardiomyopathy may have a relatively normal pulmonary vascular bed early in the course of disease. Fluffy perihilar pulmonary markings suggestive of venous congestion and acute pulmonary edema are seen only with more severe degrees of heart failure. Cardiac enlargement is often noted as an unexpected finding on a chest roentgenogram performed to evaluate for a possible pulmonary infection, bronchiolitis, or asthma.

Chamber hypertrophy noted by electrocardiography may be helpful in assessing the cause of heart failure but does not establish the diagnosis. In cardiomyopathies, left or right ventricular ischemic changes may correlate with other noninvasive parameters of ventricular function. Low-voltage QRS morphologic characteristics with ST-T-wave abnormalities may also suggest myocardial inflammatory disease, but liver is a more reliable sign. Edema may be generalized and usually involves the eyelids as well as the sacrum and less often the legs and feet. The differential diagnosis is age dependent (Table 442-1).

### Table 442-1: Etiology of Heart Failure

| **FETAL** | Severe anemia (hemolysis, fetal-maternal transfusion, parvovirus B19–induced anemia, hypoplastic anemia) |
| **PREMATUR NEONATE** | Fluid overload |
| **FULL-TERM NEONATE** | Asphyxial cardiomyopathy |
| **INFANT-TODDLER** | Left-to-right cardiac shunts (ventricular septal defect) |
| **CHILD-adolescent** | Rheumatic fever |
| **TREATMENT** | The underlying cause of cardiac failure must be removed or alleviated if possible. If the cause is a congenital cardiac anomaly amenable to surgery, medical treatment of the heart failure is indicated to prepare the patient for surgery. With today's excellent outcomes of primary surgical repair of congenital heart defects, even in the neonatal period, few children require aggressive heart failure management to "grow big enough for surgery." In contrast, if the cause of heart failure is cardiomyopathy, medical management provides temporary relief from symptoms and may allow the patient to recover if the insult is reversible (e.g., myocarditis). If the lesion is not reversible, heart failure management usually allows the child to return to normal activities for some period and delay, sometimes for months or years, the need for heart transplantation.

**General Measures**

Strict bed rest is rarely necessary except in extreme cases, but it is important that the child be allowed to rest during the day as needed and sleep adequately at night. Some older patients feel better sleeping in a semi-upright position, using several pillows (orthopnea). For infants with heart failure, an infant chair may be advisable. After patients begin to respond to treatment, restrictions on activities can often be modified within the context of the specific diagnosis and the patient's ability. Formal cardiopulmonary exercise testing can be used to assess the patient's ability to perform exercise in a controlled environment and is useful for recommending rational exercise restrictions. For patients with pulmonary edema, positive pressure ventilation may be required along with other drug therapy. For those in low-output heart failure, positive pressure ventilation can significantly reduce total body oxygen consumption by eliminating the work of breathing, and help to reverse metabolic acidosis. β-Adrenergic agonists such as dopamine, dobutamine, and epinephrine are usually used in combination.

Arterial oxygen levels may be decreased when ventilation–perfusion inequalities occurs secondary to pulmonary edema. When heart failure is severe, respiratory or metabolic acidosis, or both, may be present. Infants with heart failure often display hypotension as a result of renal water retention. Chronic diuretic treatment can decrease serum sodium levels further. Serum B-type natriuretic peptide, a cardiac neurohormone released in response to increased ventricular wall tension, is elevated in adult patients with congestive heart failure. In children, B-type natriuretic peptide may be elevated in patients with heart failure as a result of systolic dysfunction (cardiomyopathy), as well as in children with volume overload (left-to-right shunts such as ventricular septal defect).
with phosphodiesterase inhibitors such as milrinone. If the blood pressure will allow, afterload-reducing agents (nitroprusside, angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs]) may be beneficial. These agents are initiated in an intensive care setting with proper invasive monitoring of central venous and arterial blood pressure.

**Diuretics**

Infants with heart failure usually fail to thrive because of a combination of increased metabolic demands and decreased caloric intake. Increasing daily calories is an important aspect of their management. Increasing the number of calories per ounce of infant formula (or supplementing breastfeeding) may be beneficial. Many infants do not tolerate an increase beyond 24 calories/oz because of diarrhea or because these formulas provide too large a solute load for compromised kidneys.

Severely ill infants and children may lack sufficient strength for effective sucking because of extreme fatigue, rapid respirations, and generalized weakness. In these circumstances, nasogastric feedings may be helpful. In many patients with cardiac enlargement, gastroesophageal reflux is a major problem. The use of continuous drip nasogastric feedings at night, administered by pump, may improve caloric intake while decreasing problems with reflux. Occasionally, especially in infants with heart failure caused by complex congenital heart disease, medical or surgical intervention to correct reflux is necessary (Nissen fundoplication). Continued malnutrition may be an important factor in the decision to undertake earlier surgical intervention in patients who have an operable congenital heart lesion or for listing for transplantation in patients with cardiomyopathy.

The use of low-sodium formulas in the routine management of infants with heart failure is not recommended because these preparations are often poorly tolerated and may exacerbate diuretic-induced hyponatremia. Human breast milk is the ideal low-sodium nutritional source. The use of more potent diuretic agents allows more palatable standard formulas to be used for nutrition while controlling salt and water balance by chronic diuretic administration. Most older children can be managed with “no added salt” diets and abstinence from foods containing large amounts of sodium. A strict, extremely-low-sodium diet is rarely required, and rarely adhered to.

**Diuretics**

These agents interfere with reabsorption of water and sodium by the kidneys, which results in a reduction in circulating blood volume and thereby reduces pulmonary fluid overload and venricular filling pressure. Diuretics are usually the first mode of therapy initiated in patients with congestive heart failure.

**Furosemide** is the most commonly used diuretic in pediatric patients with heart failure. It inhibits the reabsorption of sodium and chloride in the distal tubules and the loop of Henle. Patients requiring acute diuresis should be given intravenous or intramuscular furosemide at an initial dose of 1-2 mg/kg, which usually results in rapid diuresis and prompt improvement in clinical status, particularly if symptoms of pulmonary congestion are present. Chronic furosemide therapy is then prescribed at a dose of 1-4 mg/kg/24 hr given between 1 and 4 times a day. Careful monitoring of electrolytes is necessary with long-term furosemide therapy because of the potential for significant loss of potassium. Potassium chloride supplementation is usually required unless the potassium-sparing diuretic spironolactone is given concomitantly. Chronic administration of furosemide may cause contraction of the extracellular fluid compartment and result in “contraction alkalosis” (see Chapter 55.7). Diuretic-induced hyponatremia may become difficult to manage in patients with severe heart failure.

**Spironolactone** is an inhibitor of aldosterone and enhances potassium retention, often eliminating the need for oral potassium supplementation, which is frequently poorly tolerated. This drug is usually given orally in 2 divided doses of 2 mg/kg/24 hr. Combinations of spironolactone and chlorothiazide are sometimes used for convenience. Adults with heart failure have improved survival when an aldosterone inhibitor is included in the diuretic regimen.

**Chlorothiazide** is also used for diuresis in children with heart failure. It is less immediate in action and less potent than furosemide, and it affects the reabsorption of electrolytes in the renal tubules only. The usual dose is 10-40 mg/kg/24 hr in 2 divided doses. Potassium supplementation is often required if this agent is used alone.

**Afterload Reducers, Including Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers**

These 2 groups of drugs reduce ventricular afterload by decreasing peripheral vascular resistance and thereby improving myocardial performance. Some of these agents also decrease systemic venous tone, which significantly reduces preload. Afterload reducers are especially useful in children with heart failure secondary to cardiomyopathy and in patients with severe mitral or aortic insufficiency. They may also be effective in patients with heart failure caused by left-to-right shunts. They are not generally used in the presence of stenotic lesions of the left ventricular outflow tract because of concern over coronary perfusion. ACEIs and ARBs may have additional beneficial effects on cardiac remodeling independent of their influence on afterload by directly influencing cardiac intracellular signaling pathways. In adult patients with dilated cardiomyopathy, the addition of an ACEI to standard medical therapy reduces both morbidity and mortality. Afterload-reducing agents are most often used in conjunction with other anticongestive drugs such as diuretics and, in some patients, digoxin.

Intravenously administered agents such as nitroprusside should be administered only in an intensive care setting and for as short a time as possible. Nitroprusside’s short intravenous half-life makes it ideal for titrating the dose in critically ill patients. Peripheral arterial vasodilation and afterload reduction are the major effects, but venodilation causing a decrease in venous return to the heart may also be beneficial. Blood pressure must be continuously monitored because sudden hypotension can occur. Consequently, nitroprusside is contraindicated in patients with preexisting hypotension. As the drug is metabolized, small amounts of circulating cyanide are produced and detoxified in the liver to thiocyanate, which is excreted in urine. When high doses of nitroprusside are administered for several days, toxic symptoms related to thiocyanate poisoning may occur (fatigue, nausea, disorientation, acidosis, and muscular spasm). If nitroprusside use is prolonged, blood thiocyanate levels should be monitored. Phosphodiesterase inhibitors (see later) are also excellent, although somewhat less-potent afterload-reducing agents, without the toxicity of nitroprusside.

The orally active ACEIs captopril and enalapril produce arterial dilation by blocking the production of angiotensin II, thereby resulting in significant afterload reduction. Venodilation and consequent preload reduction also have been reported. In addition, these agents interfere with aldosterone production and therefore also help control salt and water retention. ACEIs have additional beneficial effects on cardiac structure and function that may be independent of their effect on afterload. The oral dose for captopril is 0.3-6 mg/kg/24 hr given in 3 divided doses; for enalapril the oral dose is 0.05-0.5 mg/kg/24 hr given in 1 or 2 daily doses. Adverse reactions to ACEIs include hypotension and its sequelae (weakness, dizziness, syncope) and hyperkalemia. A maculopapular pruritic rash is encountered in a small number of patients, but the drug may be continued because the rash often disappears spontaneously with time. Neutropenia, renal toxicity, and chronic cough also occur.

**Digitalis Glycosides**

Digoxin, once the mainstay of heart failure management in both children and adults, is currently used less frequently, as a result of the introduction of newer therapies and the recognition of its potential toxicities. Many cardiologists will use digitalis as an adjunct to ACEIs and diuretics in patients with symptomatic heart failure, whereas others have moved away from its use altogether. Despite multiple clinical studies, predominantly in adults, the controversy over digitalis remains.
Digoxin is the digitalis glycoside used most often in pediatric patients. It has a half-life of 36 hr and it is absorbed well by the gastrointestinal tract (60-85%), even in infants. An initial effect can be seen as early as 30 min after administration, and the peak effect for oral digoxin occurs at ≈2-6 hr. When the drug is administered intravenously, the initial effect is seen in 15-30 min, and the peak effect occurs at 1-4 hr. The kidney eliminates digoxin, so dosing must be adjusted according to the patient’s renal function. The half-life of digoxin may be up to 6 days in patients with anuria because slower hepatic excretion pathways are used in these patients.

Rapid digitalization of infants and children in heart failure may be carried out intravenously. The dose depends on the patient’s age (Table 442-2). The recommended digitalization schedule is to give half the total digitalizing dose immediately and the succeeding 2 one-quarter doses at 12-hr intervals later. The electrocardiogram must be closely monitored and rhythm strips obtained before each of the 3 digitalizing doses. Digoxin should be discontinued if a new rhythm disturbance is noted. Prolongation of the P-R interval is not necessarily an indication to withhold digitalis, but a delay in administering the next dose or a reduction in the dosage should be considered, depending on the patient’s clinical status. Minor ST segment or T-wave changes are commonly noted with digitalis administration and should not affect the digitalization regimen. Baseline serum electrolyte levels should be measured before and after digitalization. Hypokalemia and hypercalcemia exacerbate digitalis toxicity. Because hypokalemia is relatively common in patients receiving diuretics, potassium levels should be monitored closely in those receiving a potassium-wasting diuretic in combination with digitalis. In patients with active myocarditis, some cardiologists recommend avoiding digitalis altogether and if used, maintenance digitalis should be started at half the normal dose without digitalization due to the increased risk of arrhythmia in these patients.

Patients who are not critically ill may be given digitalis initially by the oral route, and in most instances digitalization is completed within 24 hr. When slow digitalization is desirable, for example, in the

### Table 442-2: Dosage of Drugs Commonly Used for the Treatment of Congestive Heart Failure

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIGOXIN</strong></td>
<td></td>
</tr>
<tr>
<td>Digitalization (½ initially, followed by ½ q12h × 2)</td>
<td>Premature: 20 µg/kg</td>
</tr>
<tr>
<td></td>
<td>Full-term neonate (up to 1 mo): 20-30 µg/kg</td>
</tr>
<tr>
<td></td>
<td>Infant or child: 25-40 µg/kg</td>
</tr>
<tr>
<td></td>
<td>Adolescent or adult: 0.5-1 mg in divided doses</td>
</tr>
<tr>
<td></td>
<td>NOTE: These doses are PO; IV dose is 75% of PO dose</td>
</tr>
<tr>
<td></td>
<td>5-10 µg/kg/day, divided q12h</td>
</tr>
<tr>
<td></td>
<td>Trough serum level: 1.5-3.0 ng/mL &lt;6 mo old; 1-2 ng/mL &gt;6 mo old</td>
</tr>
<tr>
<td></td>
<td>NOTE: These doses are PO; IV dose is 75% of PO dose</td>
</tr>
<tr>
<td>Maintenance digoxin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIURETICS</strong></td>
<td></td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>IV: 0.5-2 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>PO: 1-4 mg/kg/day, divided qd-qid</td>
</tr>
<tr>
<td>Bumetanide (Bumex)</td>
<td>IV: 0.01-0.1 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>PO: 0.01-0.1 mg/kg/day q24-48h</td>
</tr>
<tr>
<td>Chlorthalidone (Diuril)</td>
<td>PO: 20-40 mg/kg/day, divided bid or tid</td>
</tr>
<tr>
<td>Spironolactone (Aldactone)</td>
<td>PO: 1-3 mg/kg/day, divided bid or tid</td>
</tr>
<tr>
<td>Nesiritide (B-type natriuretic peptide)</td>
<td>IV: 0.001-0.03 µg/kg/min</td>
</tr>
<tr>
<td><strong>ADRENERGIC AGONISTS (ALL IV)</strong></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2-20 µg/kg/min</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2-30 µg/kg/min</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0.01-0.5 µg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.1-1.0 µg/kg/min</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.1-2.0 µg/kg/min</td>
</tr>
<tr>
<td><strong>PHOSPHODIESTERASE INHIBITORS (ALL IV)</strong></td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>0.25-1.0 µg/kg/min</td>
</tr>
<tr>
<td><strong>AFTERLOAD-REDUCING AGENTS</strong></td>
<td></td>
</tr>
<tr>
<td>Captopril (Capoten), all PO</td>
<td>Prematures: start at 0.01 mg/kg/day; 0.1-0.4 mg/kg/day, divided q6-24h</td>
</tr>
<tr>
<td></td>
<td>Infants: 1.5-6 mg/kg/day, divided q6-12h</td>
</tr>
<tr>
<td>Enalapril (Vasotec), all PO</td>
<td>Children: 2.5-6 mg/kg/day, divided q6-12h</td>
</tr>
<tr>
<td>Hydralazine (Apresoline)</td>
<td>0.08-0.5 mg/kg/day, divided q12-24h</td>
</tr>
<tr>
<td></td>
<td>IV: 0.1-0.5 mg/kg/dose (maximum: 20 mg)</td>
</tr>
<tr>
<td></td>
<td>PO: 0.75-5 mg/kg/day, divided q6-12h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>IV: 0.25-0.5 µg/kg/min start; increase to 20 µg/kg/min maximum</td>
</tr>
<tr>
<td>Nitropresside (Nipride)</td>
<td>IV: 0.5-8 µg/kg/min</td>
</tr>
<tr>
<td><strong>β-ADRENERGIC BLOCKERS</strong></td>
<td></td>
</tr>
<tr>
<td>Carvedilol (Coreg)</td>
<td>PO: initial dose 0.1 mg/kg/day (maximum: 6.25 mg) divided bid, increase gradually (usually 2 wk intervals) to maximum of 0.5-1 mg/kg/day over 8-12 wk as tolerated; adult maximal dose: 50-100 mg/day</td>
</tr>
<tr>
<td>Metoprolol (Lopressor, Toprol-XL)</td>
<td>PO, nonextended release form: 0.2 mg/kg/day divided bid, increase gradually (usually 2 wk intervals) to maximum dose of 1-2 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>PO, extended release form (Toprol-XL) is given once daily; adult initial dose 25 mg/day, maximum dose is 200 mg/day</td>
</tr>
</tbody>
</table>

Note: Pediatric doses based on weight should not exceed adult doses. Because recommendations may change, these doses should always be double-checked. Doses may also need to be modified in any patient with renal or hepatic dysfunction.

Maintenance digitalis therapy is started ≈12 hr after full digitalization. The daily dosage, one quarter of the total digitalizing dose, is divided in 2 and given at 12-hr intervals. The oral maintenance dose is usually 20-25% higher than when digoxin is used parenterally (see Table 442-2). The normal daily dose of digoxin for older children (≥3 yr of age) calculated by body weight should not exceed the usual adult dose of 0.125-0.5 mg/24 hr.
Phosphodiesterase Inhibitors

Milrinone is useful in treating patients with low cardiac output who are refractory to standard therapy and has been shown to be highly effective in managing the low-output state present in children after open heart surgery. It works by inhibition of phosphodiesterase, which prevents the degradation of intracellular cyclic adenosine monophosphate. Milrinone has both positive inotrop effects on the heart and peripheral vasodilatory effects and has generally been used as an adjunct to dopamine or dobutamine therapy in the intensive care unit. It is given by intravenous infusion at 0.25-1 µg/kg/min, sometimes with an initial loading dose of 50 µg/kg. A major side effect is hypotension secondary to peripheral vasodilation, especially when a loading dose is used. The hypotension can generally be managed by the administration of intravenous fluids to restore adequate intravascular volume.

Chronic Treatment with β-Blockers

Studies in adults with dilated cardiomyopathy show that β-adrenergic blocking agents, introduced gradually as part of a comprehensive heart failure treatment program, improve exercise tolerance, decrease hospitalizations, and reduce overall mortality. The agents most often used are carvedilol, an agent with both α- and β-adrenergic receptor blocking as well as free radical scavenging effects and metoprolol, a β₁-adrenergic receptor selective antagonist. β-Blockers are used for the chronic treatment of patients with heart failure and should not be administered when patients are still in the acute phase of heart failure (i.e., receiving intravenous adrenergic agonist infusions). Although very efficacious in adults, clinical studies in children have shown mixed results, potentially due to the significant heterogeneity of the populations being studied and differences in the types of β-blocking agents.

ELECTROPHYSIOLOGIC APPROACHES TO HEART FAILURE MANAGEMENT

Significant improvements in symptomatology and functional capacity have been achieved in selected adult patients with cardiomyopathy using biventricular resynchronization pacing. This technique improves cardiac output by restoring normal synchrony between right and left ventricular contraction, which is often lost in patients with dilated cardiomyopathy (these patients usually manifest a left bundle branch block on electrocardiogram). There is growing experience with resynchronization pacing in children and reports show early success in patients with left ventricular failure (in the setting of cardiomyopathy), right ventricular failure (in the setting of previously repaired tetralogy of Fallot), and somewhat less so in patients with single ventricular failure (in the setting of complex congenital heart disease).

Arrhythmia is a leading cause of sudden death in patients with severe cardiomyopathy (both dilated and hypertrophic). Although antiarrhythmic medications can sometimes reduce this risk, for patients at particularly high risk (e.g., those with a condition known to be associated with a high risk of ventricular arrhythmia or those who have already experienced a “missed sudden death” episode), use of an implantable cardioverter-defibrillator can be lifesaving (see Chapter 429).

442.1 Cardiogenic Shock

Daniel Bernstein

Cardiogenic shock (see Chapter 70) may occur as a complication of (1) severe cardiac dysfunction before or after cardiac surgery, (2) sepsisemia, (3) severe burns, (4) anaphylaxis, (5) cardiomyopathy, (6) myocarditis, (7) myocardial infarction or stunning, and (8) acute central nervous system disorders. It is characterized by low cardiac output and hypotension, and therefore results in inadequate tissue perfusion.

Treatment is aimed at reinstitution of adequate cardiac output to prevent the untoward effects of prolonged ischemia on vital organs, as
Table 442-3  Treatment of Cardiogenic Shock

<table>
<thead>
<tr>
<th>DETERMINANTS OF STROKE VOLUME</th>
<th>Preload</th>
<th>Contractility</th>
<th>Afterload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters measured</td>
<td>CVP, PCWP, LAP, cardiac chamber size on echocardiography</td>
<td>CO, BP, fractional shortening or ejection fraction on echocardiography, MV ( \text{O}_2 ) saturation</td>
<td>BP, peripheral perfusion, SVR</td>
</tr>
<tr>
<td>Treatment to improve cardiac output</td>
<td>Volume expansion (crystalloid, colloid, blood)</td>
<td>( \beta )-Adrenergic agonists, phosphodiesterase inhibitors</td>
<td>Afterload-reducing agents: milrinone, nitroprusside, ACE inhibitors</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; BP, blood pressure; CO, cardiac output (measured with a thermodilution catheter); CVP, central venous pressure; LAP, left atrial pressure (measured with an indwelling LA line); MV \( \text{O}_2 \) saturation, mixed venous oxygen saturation (measured with a central venous catheter); PCWP, pulmonary capillary wedge pressure (measured with a thermodilution catheter); SVR, systemic vascular resistance (calculated from CO and mean BP).

*The goal is to improve peripheral perfusion by increasing cardiac output, where: cardiac output = heart rate x stroke volume.

well as management of the underlying cause. Under normal physiologic conditions, cardiac output is increased as a result of sympathetic stimulation, which increases both contractility and heart rate. If contractility is depressed, cardiac output can be improved by increasing heart rate, increasing ventricular filling pressure (preload) through the Frank-Starling mechanism, or by decreasing systemic vascular resistance (afterload). Optimal filling pressure is variable and depends on a number of extracardiac factors, including ventilatory support and intra-abdominal pressure. The increased pressure necessary to fill a relatively noncompliant ventricle should also be considered, particularly after open heart surgery, or in patients with restrictive or hypertrophic cardiomyopathies. If carefully administered incremental fluid does not result in improved cardiac output, abnormal myocardial contractility or an abnormally high afterload, or both, must be implicated as the cause of the low cardiac output. Although tachycardia is one mechanism to increase cardiac output, an excessive increase in heart rate may reduce cardiac output because of decreased time for diastolic filling.

Myocardial contractility usually improves when treatment of the basic cause of shock is instituted, hypoxia is eliminated, and acidosis is corrected. \( \beta \)-Adrenergic agonists such as dopamine, epinephrine, and dobutamine improve cardiac contractility, increase heart rate, and ultimately increase cardiac output. However, some of these agents also have \( \alpha \)-adrenergic effects, which cause peripheral vasoconstriction and increase afterload, so careful consideration of the balance of these effects in an individual patient is important. The use of cardiac glycosides to treat acute low cardiac output states should be avoided.

Patients in cardiogenic shock may have a marked increase in systemic vascular resistance resulting in high afterload and poor peripheral perfusion. If the increased systemic vascular resistance is persistent and the administration of positive inotropic agents alone does not improve tissue perfusion, the use of afterload-reducing agents may be appropriate, for example, nitroprusside or milrinone in combination with a \( \beta \)-adrenergic agonist. Milrinone, which acts through inhibition of phosphodiesterase is also a positive inotropic agent, and combined with a \( \beta \)-adrenergic agonist, works synergistically to increase levels of myocardial cyclic adenosine monophosphate.

Sequential evaluation and management of cardiovascular shock are mandatory (see Chapter 70). Table 442-3 outlines the general treatment principles for acute cardiac circulatory failure under most circumstances. Treatment of infants and children with low cardiac output after cardiac surgery also depends on the nature of the operative procedure, any intraoperative complications, and the physiology of the circulation after repair or palliation (see Chapter 428). If cardiogenic shock does not respond rapidly to medical therapy, consideration of mechanical support is warranted. Modalities available for pediatric patients include extracorporeal membrane oxygenation for short-term support, and left and right ventricular assist devices for longer-term support.

Bibliography is available at Expert Consult.
Bibliography


Pediatric heart transplantation is standard therapy for children with end-stage cardiomyopathy and other lesions not amenable to surgical repair. As of 2010, >7,500 heart transplants had been performed on children in the United States and Europe, with ≈500 transplants annually; a quarter of these being performed on children <1 yr of age. Survival rates among children compare favorably with those of adults. For children transplanted in the 1980s and early 1990s, 1 yr survival has been 75-80%, whereas for those transplanted after 2000, 1 yr survival is now in the range of 90%; during the same time periods, 5 yr survival has improved from 60-65% to 75% (Fig. 443-1). A growing number of children are now reaching their 15, 20, and 30 yr posttransplant anniversaries.

INDICATIONS
Heart transplantation is performed in infants and children with end-stage cardiomyopathy who have become refractory to medical therapy, in patients with previously repaired or palliated congenital heart disease who have developed ventricular dysfunction or other nonoperable late-term complications, and (less frequently) in patients with complex congenital heart disease (pulmonary atresia with intact septum and coronary arterial stenoses, some forms of hypoplastic left heart syndrome) for whom standard surgical procedures are extremely high risk. Cardiomyopathies account for >50% of heart transplants in pediatric patients older than 1 yr, with the percentage of patients with previously repaired complex congenital heart lesions at ~30%. In infants younger than 1 yr, congenital heart lesions used to represent >80% of transplants; this fraction has dropped to ~60% as standard surgical results for complex congenital heart disease (hypoplastic left heart syndrome) have improved.

RECIPIENT AND DONOR SELECTION
Potential heart transplant recipients must be free of serious noncardiac medical problems such as neurologic disease, active systemic infection, severe hepatic or renal disease, and severe malnutrition. Many children with ventricular dysfunction are at risk for the development of pulmonary vascular disease, which if severe enough would preclude heart transplantation. Therefore, pulmonary vascular resistance is measured
at cardiac catheterization in heart transplant candidates, both at rest and, if elevated, in response to vasodilators. Patients with fixed elevated pulmonary vascular resistance are at higher risk for heart transplantation and may be considered candidates for either heterotopic heart transplantation (see later) or heart-lung transplantation (see Chapter 443.2). However, with recent advances in postoperative management of pulmonary hypertension (e.g., inhaled nitric oxide), many patients with moderate elevations in pulmonary vascular resistance can undergo heart transplant alone. A comprehensive social services evaluation is an important component of the recipient evaluation. Because of the complex posttransplantation medical regimen, the family must have a history of compliance. Detailed informed consent indicating that the family (and if old enough, the patient) understand the lifelong commitment to immunosuppressive medication and careful monitoring, must be obtained.

Donor shortage is a serious problem for both adults and children. At the national registry of transplant recipients in the United States (the United Network for Organ Sharing [UNOS]), allografts are matched by ABO blood group and body weight. HLA matching is not currently performed unless the recipient has preformed antibodies against a particular HLA antigen, in which case a prospective crossmatch can be obtained. ABO matching may not be required for young infants; the exact age under which ABO tolerance develops has not yet been determined. Contraindications to organ donation include prolonged cardiac arrest with persistent moderate to severe cardiac dysfunction, ongoing systemic illness or infection, and preexisting severe cardiac disease. Physicians caring for a patient who may be a potential donor should always contact the organ donor coordinator at their institution, who can best judge the appropriateness of organ donation and has experience in interacting with potential donor families. A history of resuscitation alone or reparable congenital heart disease is not an automatic exclusion for donation.

The decision of when to place a patient on the transplant waiting list is based on a combination of many factors, including poor ventricular function, markedly decreased exercise tolerance as determined by cardiopulmonary exercise testing (see Chapter 423.3), poor response to medical anticongestive therapy, multiple hospitalizations for heart failure, arrhythmia, progressive deterioration in renal or hepatic function, early stages of pulmonary vascular disease, and poor nutritional status. In patients awaiting transplantation, those with poor left ventricular function are usually started on a regimen of anticoagulation to reduce the risk of mural thrombosis and thromboembolism. Patients with low cardiac output resulting in decreases in end-organ (renal or hepatic) function unresponsive to standard pharmacologic treatment, or those that require chronic assisted ventilation or high-dose inotropic agents are now considered candidates for placement of left ventricular or biventricular assist devices, which can stabilize hemodynamics, improve renal and hepatic function, allow for extubation, and serve as a bridge to transplantation (see Chapter 442). The more recent availability of ventricular assist devices (e.g., the Berlin Heart EXCOR) that are small enough to support young infants has revolutionized the approach to supporting pediatric patients awaiting cardiac transplantation. The role of extracorporeal membrane oxygenation (ECMO) for these patients has been reduced; the need for ECMO support is still a risk factor for poorer outcomes after transplant. There is now limited but growing experience with totally implantable artificial heart devices in older children and adolescents, used either as a bridge to transplant, or in cases (e.g., children with peripheral muscular disorders) where transplantation would be a much higher risk.

**PERIOPERATIVE MANAGEMENT**

In the classic operation, both donor and recipient hearts were excised so that the posterior portions of the atria containing the venae cavae and pulmonary veins are left intact. The aorta and pulmonary artery are divided above the level of the semilunar valves. The anterior portion of the donor’s atria was then connected to the remaining posterior portion of the recipient’s atria, thereby avoiding the need for delicate suturing of the venae cavae or pulmonary veins. The donor and recipient great vessels were connected via end-to-end anastomoses. This has largely been supplanted by the bicaval anastomosis, with the donor right atrium (and sinus node) left intact and the suture lines at the superior and inferior vena cavae; the left atrial connection is still performed as in the classic procedure. Heterotopic heart transplantation has been used occasionally for patients with left ventricular cardiomyopathy and elevated pulmonary vascular resistance. In this operation, the donor and recipient hearts are connected in parallel so that the recipient right ventricle (which has hypertrophied over time as a result of the elevated pulmonary pressures) pumps mostly to the lungs, and the donor left ventricle pumps mostly to the body. This operation may be preferable to heart-lung transplant for appropriate candidates (patients with pulmonary hypertension but without parenchymal lung disease, without evidence of right ventricular failure, and without serious congenital heart disease), as it is associated with a greater survival at all posttransplant time points.

In the immediate postoperative period, immunosuppression is achieved with either a triple- or double-drug regimen, with more centers adopting a minimal steroid or steroid-free regimen. The most common combinations are a calcineurin inhibitor (either cyclosporine or tacrolimus) plus a white blood cell enzyme inhibitor (mycophenolate mofetil or azathioprine), plus or minus prednisone. In many centers, induction therapy (usually an antilymphocyte preparation) is added in the 1st wk, either antithymocyte globulin (ATG) or the humanized anti–interleukin 2 receptor antibodies (basiliximab). In children who do not experience significant graft rejection, steroids can be gradually eliminated after the 1st 6-12 mo. Some centers do not use steroids as part of maintenance immunosuppression, but do use them as bolus treatment for acute rejection episodes.

Most pediatric heart transplant recipients can be extubated within the 1st 48 hr after transplantation and are out of bed within 3-4 days. These patients are often discharged within the 1st 2 wk after transplantation. In patients with preexisting high-risk factors, postoperative recovery may be considerably prolonged. For those with preoperative pulmonary hypertension, the use of nitric oxide in the postoperative period can buy time to allow the donor right ventricle to hypertrophy in response to elevated pulmonary artery pressures. Occasionally, these patients will require right ventricular assist device support.

**DIAGNOSIS AND MANAGEMENT OF ACUTE GRAFT REJECTION**

Posttransplantation management consists of adjusting medications to maintain a balance between the risk of rejection and the side effects of over-immunosuppression. Along with infection, acute graft rejection is a leading cause of death in pediatric heart transplant...
recipients. The incidence of acute rejection is greatest in the 1st 3 mo after transplantation and decreases considerably thereafter. Many pediatric patients experience at least 1 episode of acute rejection in the 1st 2 yr after transplantation, although modern immunosuppressive regimens have decreased the frequency of serious rejection episodes. Because the symptoms of rejection can mimic many routine pediatric illnesses (pneumonia, gastroenteritis), *it is mandatory that the transplant center be notified whenever a heart transplant recipient is seen in the pediatrician’s office or emergency room for any acute illness.*

Clinical manifestations of acute rejection may include fatigue, fluid retention, fever, diaphoresis, abdominal symptoms, and a gallop rhythm. The electrocardiogram may show reduced voltage, atrial or ventricular arrhythmias, or heart block but is usually nondiagnostic. Roentgenographic examination may show an enlarged heart, effusions, or pulmonary edema, but usually only in the more advanced stages of rejection. Most rejection episodes occur without any detectable clinical symptoms. On echocardiography, indices of systolic left ventricular function may be decreased; however, these usually do not deteriorate until rejection is at least moderately severe. Techniques to evaluate wall thickening and left ventricular diastolic function have not fulfilled their promise as predictors of early rejection. Most transplant centers do not rely on echocardiography alone for rejection surveillance.

Myocardial biopsy is the most reliable method of monitoring patients for rejection. Biopsy specimens are taken from the right ventricular side of the interventricular septum and can be harvested relatively safely, even in small infants. In older children, myocardial biopsies may be performed as often as every 1–4 wk during the 1st 3–6 mo after transplantation. The frequency is then reduced over the next 2 yr to between 2 and 4 biopsies per year unless the patient has an episode of rejection. In infants, surveillance biopsies are usually performed less often and may be as infrequent as once or twice per year. Children may have clinically unsuspected rejection episodes even 5–10 yr after transplantation; most pediatric transplant centers continue routine surveillance biopsies, albeit at less-frequent intervals (every 6–12 mo).

Criteria for grading cardiac rejection are based on a system developed by the International Society for Heart and Lung Transplantation (ISHLT); these criteria take into account the degree of cellular infiltration and whether myocyte necrosis is present. ISHLT rejection grade 1R (former grades 1A, 1B, and 2) is usually mild enough that it is often not treated with bolus steroids, and many of these episodes resolve spontaneously. A repeat biopsy specimen is often obtained within a shorter time frame. For patients with ISHLT grade 2R (formerly grade 3A) rejection, treatment is instituted with either intravenous methylprednisolone or a “bump and taper” of oral prednisone. Asymptomatic patients >3 mo posttransplant and with normal echocardiograms are often treated as outpatients. Patients with grade 3R (formerly grades 3B or 4), or anyone with hemodynamic instability, are admitted to the hospital for intravenous steroid and potentially more aggressive anti-rejection therapy. For rejection episodes resistant to steroid therapy, additional therapeutic regimens include a repeat course of an antilymphocyte preparation (antithymocyte globulin), methotrexate, or total lymphoid irradiation. Patients with repeated episodes of rejection may also benefit from being switched from cyclosporine to tacrolimus (or vice versa). Refractory rejection is not considered a good indication for retransplantation because of the relatively poor outcomes compared with other indications for retransplantation.

Gene expression profiling of peripheral blood mononuclear cells has been validated in adults as a highly sensitive, and moderately selective, method of rejection surveillance. These results have not been confirmed in children. Other current techniques which may hold promise include the profiling of donor cell free DNA released in the serum of patients during episodes of graft injury. Progress has also been made in genetic profiling as a means to determine which patients are most at risk for rejection. Children who have single-nucleotide polymorphisms leading to greater activity of inflammatory cytokines or decreased activity of regulatory cytokines are at increased risk of rejection. This type of profiling may be useful in designing patient-specific immunosuppressive regimens in the future.

Some rejection episodes are not associated with a cellular infiltrate on biopsy. These cases of acellular or humoral rejection are mediated by circulating antibodies and can be detected by immunostaining of the biopsy specimen for the complement component C4d, for macrophages expressing CD68, and for evidence of histologic damage. Humoral rejection is less responsive to standard therapies for acute cellular rejection (e.g., bolus steroids) and has been treated with plasmapheresis, intravenous immunoglobulin, the anti-CD20 monoclonal antibody rituximab, and the proteasome inhibitor bortezomib, all with mixed results.

**COMPLICATIONS OF IMMUNOSUPPRESSION**

**Infection**

Infection is 1 of the 2 leading causes of death in pediatric transplant patients (Fig. 443-2). The incidence of infection is greatest in the 1st 3 mo after transplantation when immunosuppressive doses are highest. Viral infections are the most common, which accounts for as many as 25% of infectious episodes. Cytomegalovirus (CMV) infection used to be 1 of the leading causes of morbidity and mortality and may occur as a primary infection in patients without previous exposure to the virus or as a reactivation. Severe CMV infection can be disseminated or associated with pneumonitis or gastroenteritis and may provoke an episode of acute graft rejection or graft coronary disease. Most centers use intravenous ganciclovir or CMV immune globulin (CytoGam), or both, as prophylaxis in any patient receiving a heart from a donor who is positive for CMV or in any recipient who has serologic evidence of previous CMV disease. Oral preparations of ganciclovir with improved absorption profiles are available for chronic therapy and have largely replaced intravenous preparations for prophylaxis. These regimens have significantly reduced the burden of CMV disease in heart transplant patients. Polymerase chain reaction enhances the ability to diagnose CMV infection and to monitor the efficacy of therapy serially.

Most normal childhood viral illnesses are well tolerated and do not usually require special treatment. Otitis media and routine upper respiratory tract infections can be treated in the outpatient setting, although fever or symptoms that last beyond the usual course require further investigation. Gastroenteritis, especially with vomiting, can result in markedly reduced absorption of immunosuppressive medications and provoke a rejection episode. In this setting, drug levels should be closely monitored and the use of intravenous medications considered. Gastroenteritis can also be a sign of rejection, so a high index of suspicion must always be maintained. Varicella is another childhood illness of some concern for immunosuppressed patients. If a heart transplant recipient acquires clinical varicella infection, treatment with intravenous acyclovir usually attenuates the illness.

![Figure 443-2 Major causes of death after pediatric heart transplantation by time since transplant. CAV, coronary artery vasculopathy; CMV, cytomegalovirus. (From Kirk R, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 29:1119–1128, 2010, Fig. 9.)](image-url)
Bacterial infections are the next most frequent, with the lung being the most common site of infection (35%), followed by the blood, the urinary tract, and, less commonly, the sternotomy site. Other sources of posttransplantation infection include fungi (14%) and protozoa (6%). Many centers use nystatin washout to decrease fungal colonization and trimethoprim/sulfamethoxazole (Bactrim, Septra) during the time a patient is on steroids as prophylaxis to prevent Pneumocystis carinii infection.

**Growth Retardation**
Patients requiring chronic steroid administration usually have decreased linear growth, though most pediatric transplant programs aim for steroid-free immunosuppression within the 1st yr posttransplant. In those patients who experience rejection when steroids are withdrawn, alternate-day steroid regimens result in improved linear growth. Total lymphoid irradiation has shown promise as a steroid-sparing protocol. Despite these concerns, 75% of long-term survivors of pediatric heart transplantation have normal growth.

**Hypertension**
Hypertension is common in patients treated with cyclosporine, caused by a combination of plasma volume expansion and defective renal sodium excretion. Corticosteroids usually potentiate cyclosporine-induced hypertension. Patients are typically managed with a combination of a diuretic and a vasodilator. Agents that work via calcium channel blockade have the additional advantage of possibly attenuating graft coronary disease. The incidence of hypertension is slightly lower in patients treated with tacrolimus.

**Renal Function**
Chronic administration of cyclosporine or tacrolimus can lead to a tubulointerstitial nephropathy in adults, but severe renal dysfunction is less common in children. Most pediatric patients gradually have an increase in serum creatinine in the 1st yr after transplantation; if renal dysfunction occurs, it usually responds to a decrease in calcineurin inhibitor dosage. The addition of sirolimus, a target of rapamycin inhibitor, instead of mycophenolate allows a reduction in the dose of calcineurin inhibitor in patients with renal dysfunction. Infection with BK virus, a growing problem in renal transplant patients, has been described as a source of renal dysfunction in heart transplant patients. Fortunately, pediatric heart transplant patients infrequently require renal transplantation long-term.

**Neurologic Complications**
Neurologic side effects of cyclosporine and tacrolimus include tremor, myalgias, paresthesias, and, rarely, seizures. These complications can be treated with reduced doses of medication and occasionally with oral magnesium supplementation. Intracranial infections pose a significant risk, especially because some of the more frequent signs (nuchal rigidity) may be absent in immunosuppressed patients. Potential organisms include Aspergillus, Cryptococcus neoformans, and Listeria monocytogenes. A rare form of encephalopathy, known as PRES (posterior reversible encephalopathy syndrome) can occur in patients on calcineurin inhibitors (either cyclosporine or tacrolimus). PRES presents with hypertension, headaches and seizures, requires MRI for diagnosis, and is usually managed by changing calcineurin inhibitor or in rare cases eliminating calcineurin inhibitors totally in favor of other immunosuppressive agents (e.g., sirolimus/mycophenolate).

**Tumors**
One of the serious complications limiting long-term survival in pediatric heart transplant patients is the risk of neoplastic disease. The most common is posttransplant lymphoproliferative disease (PTLD), a condition associated with Epstein-Barr virus infection. Patients who are Epstein-Barr virus seronegative at the time of transplant (usually infants and young children) are at increased risk of developing PTLD if they subsequently seroconvert, acquiring the virus either from the donor organ or from primary infection (mononucleosis). Unlike true cancer, many cases of PTLD respond to a reduction in immunosuppression plus antiviral therapy with acyclovir. A monoclonal antibody directed against the CD20 antigen on activated lymphocytes (rituximab) has been effective against some forms of PTLD. However, PTLD can behave more aggressively and many cases eventually require chemotherapy. An increased risk of skin cancer requires that children use appropriate precautions when exposed to sunlight.

**Chronic Rejection**
Graft coronary artery disease (GCAD) is a manifestation of chronic graft rejection that occurs in ~20% of children 5 yr after transplant. The cause is still unclear, although it is thought to be a form of immunologically mediated vessel injury (chronic rejection). Hypercholesterolemia and hyperglycemia are thought to increase the risk of this disease. Unlike native coronary atherosclerosis, GCAD is a diffuse process with a high degree of distal vessel involvement. Because the transplanted heart has been denervated, patients may not experience symptoms such as angina pectoris during ischemic episodes, and the initial manifestation may be cardiovascular collapse or sudden death. Most centers perform coronary angiography annually to screen for coronary abnormalities; some also perform coronary intravascular ultrasound on adolescents. Standard coronary artery bypass procedures are usually not helpful because of the diffuse nature of the process, although transcatheter stenting can sometimes be effective for isolated lesions. For severe cases, repeat heart transplantation has been the only effective treatment. Thus, prevention has been the focus of most current research. The cell-cycle inhibitors sirolimus and everolimus have been shown to decrease coronary arterial intimal thickening in adult transplant patients. Other drugs that have been shown to reduce the risk of GCAD include the calcium channel blockers (such as diltiazem) and the cholesterol-lowering HMG-CoA (3-hydroxy-3-methyl-coenzyme A) reductase inhibitors (such as pravastatin or atorvastatin).

**Other Complications**
Corticosteroids usually result in cushingoid facies, steroid acne, and striae. Cyclosporine can cause a subtle change in facial features such as hypertrichosis and gingival hyperplasia. These cosmetic features can be particularly disturbing to adolescents and may be the motivation for noncompliance, one of the leading risks for late morbidity and mortality. Most of these cosmetic complications are dose related and improve as immunosuppressive medications are weaned. Osteoporosis and aseptic necrosis are additional reasons for reducing the steroid dosage as soon as possible. Diabetes and pancreatitis are rare but serious complications.

**Rehabilitation**
Despite the potential risks of immunosuppression, the prospect for rehabilitation in pediatric heart transplant recipients is excellent. More than 95% of pediatric heart transplant recipients have no functional limitations in their daily lives. The majority of patients do not require rehospitalization for transplant-related problems. Pediatric heart transplant recipients can attend daycare or school and participate in non-collision competitive sports (no tackle football or martial arts) and other age-appropriate activities. Standardized measurements of ventricular function are close to normal. Because the transplanted heart is denervated, the increase in heart rate and cardiac output during exercise is slower in transplant recipients, and maximal heart rate and cardiac output responses are mildly attenuated. These subtle abnormalities are rarely noticeable by the patient.

Growth of the transplanted heart is excellent, although a mild degree of ventricular hypertrophy is commonly seen, even years after transplantation. The sites of atrial and great vessel anastomoses usually grow without the development of obstruction. In neonates who undergo transplantation for hypoplastic left heart syndrome, however, juxta- ductal aortic coarctation may recur.

As assessed by standardized testing, the psychologic adjustment to heart transplantation in children is usually good. However, a serious problem with noncompliance often occurs once patients reach
adolescence, and life-threatening rejection may result. Early intervention by social workers, counselors, and psychologists may be able to reduce this risk.

Bibliography is available at Expert Consult.

443.2 Heart-Lung and Lung Transplantation
Daniel Bernstein

More than 670 heart-lung and 1,700 lung (single or double) transplants have been performed in children in the United States and Europe, with ≈140 procedures performed annually. Primary indications for heart-lung transplantation include cystic fibrosis, primary pulmonary hypertension, complex congenital heart disease with pulmonary hypoplasia or Eisenmenger syndrome, congenital lung abnormalities, and end-stage parenchymal lung disease (bronchopulmonary dysplasia, chronic lung disease, and interstitial fibrosis). Many of these patients with normal hearts are candidates for single- or double-lung transplantation if right ventricular function is preserved and there has been a trend towards decreasing combined heart-lung transplant for this reason. In some patients with Eisenmenger physiology, double-lung transplantation can be performed in combination with repair of intracardiac defects. Patients with cystic fibrosis are not candidates for single-lung grafts because of the risk of infection from the diseased contralateral lung. Patients are selected according to many of the same criteria as for heart transplant recipients (see Chapter 443.1).

Posttransplant immunosuppression is usually achieved with a triple-drug regimen, combining a calcineurin inhibitor (cyclosporine or tacrolimus) with a white blood cell enzyme inhibitor (mycophenolate or azathioprine) and prednisone. Most patients receive induction therapy with an antithymocyte or anti-T cell preparation. Unlike patients with isolated heart transplants, patients with heart or heart-lung transplants cannot be weaned totally off steroids. Prophylaxis against \( P \). \textit{carinii} infection is achieved with trimethoprim-sulfamethoxazole or aerosolized pentamidine. Ganciclovir and CMV immune globulin prophylaxis are used as in heart transplant recipients (see Chapter 443.1).

Pulmonary rejection is common in lung or heart-lung transplant recipients, whereas heart rejection is encountered much less often than in patients with isolated heart transplants. Symptoms of lung rejection may include fever and fatigue, although many episodes are minimally symptomatic. Surveillance for rejection is performed by monitoring pulmonary function (forced vital capacity; forced expiratory volume in 1 sec \( [\text{FEV}_1] \);forced expiratory flow, midexpiratory phase \( [\text{FEF}_{25-75\%}] \)); systemic arterial oxygen tension, and chest roentgenograms and by transbronchial biopsy.

Actuarial survival rates after lung or heart-lung or lung transplantation in children are currently 75% at 1 yr and 50% at 5 yr; improved patient selection and postoperative management are continually improving these survival statistics from prior eras. Graft failure and infection are the leading cause of early death, whereas a form of chronic rejection known as \textit{bronchiolitis obliterans} accounts for nearly 50% of late mortality. Other causes of early morbidity and mortality include tracheal complications, pulmonary venous obstruction, donor lung dysfunction, bleeding, and acute rejection. Additional late complications include the development of airway stenosis, late graft failure, PTLD, and other side effects of chronic immunosuppression.

Postoperative indices of cardiopulmonary function and exercise capacity show significant improvement. Nearly 90% of patients are without activity limitations at 3 yr follow-up and more than 80% at 5 yr follow-up. Problems of donor availability are even more severe with lung transplantation than with isolated heart transplantation. Living related lung transplantation, in which a lobe from a parent is transplanted into a child, has been used to partially alleviate this problem.

Bibliography is available at Expert Consult.
Bibliography


Bibliography


Diseases of the Blood Vessels (Aneurysms and Fistulas)

444.1 Kawasaki Disease
Daniel Bernstein

See also Chapter 166.

Aneurysms of the coronary and occasionally the systemic arteries may complicate Kawasaki disease and are the leading cause of morbidity in this disease (Figs. 444-1 and 444-2). Other than in Kawasaki disease, aneurysms are not common in children and occur most frequently in the aorta in association with coarctation of the aorta, patent ductus arteriosus, Ehlers-Danlos type IV (arterial ecchymotic form), hyperimmunoglobulin E syndrome, and Marfan syndrome and in intracranial vessels (see Chapter 601). They may also occur secondary to an infected embolus; infection contiguous to a blood vessel; trauma; congenital abnormalities of vessel structure, especially the medial wall; and arteritis, for example, polyarteritis nodosa, Behçet syndrome, and Takayasu arteritis (see Chapter 167.2).

444.2 Arteriovenous Fistulas
Daniel Bernstein

Arteriovenous fistulas may be limited and small or may be extensive producing systemic complications (see Chapters 505 and 650). The most common sites in infants and children are within the cranium, in the liver, in the lung, in the extremities, and in vessels in or near the thoracic wall. These fistulas, though usually congenital, may follow trauma or be a manifestation of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Femoral arteriovenous fistulas are a rare complication of percutaneous femoral catheterization.

CLINICAL MANIFESTATIONS

Clinical symptoms occur only in association with large arteriovenous communications when arterial blood flows into a low-pressure venous system without the resistance of the capillary bed; local venous pressure is increased, and arterial flow distal to the fistula is decreased. Systemic arterial resistance falls because of the runoff of blood through the fistula. Compensatory mechanisms include tachycardia and increased stroke volume so that cardiac output rises. Total blood volume is also increased. In large fistulas, left ventricular dilation, a widened pulse pressure, and high output heart failure occur. CT, MRI, or injection of contrast material into an artery proximal to the fistula confirms the diagnosis.
Intracranial arteriovenous fistulas may be generalized or localized in the liver and may be hemangioendotheliomas or cavernous hemangiomas. The fistula may be located between the hepatic artery and the ductus venosus or portal vein. Congenital hemorrhagic telangiectasia may also be present. Large arteriovenous fistulas are associated with increased cardiac output and heart failure. Hepatomegaly is usual, and systolic or continuous murmurs may be audible over the liver.

Peripheral arteriovenous fistulas generally involve the extremities and are associated with disfigurement, swelling of the extremity, and visible hemangiomas. Some are located in areas that result in upper airway obstruction. Because only a small minority results in large arterial runoff, cardiac failure is uncommon.

**TREATMENT**

Medical management of heart failure is initially helpful in neonates with these conditions; with time, the size of the shunt may diminish and symptoms spontaneously regress. Hemangiomas of the liver often eventually disappear completely. Large liver hemangiomas have been treated with steroids, ε-aminocaproic acid, interferon, local compression, embolization, or local irradiation; the beneficial effects of these management options are not firmly established because individual patients display marked variation in clinical course without treatment. Catheter embolization is becoming the treatment of choice for many patients with a symptomatic arteriovenous fistula. Embolic agents that have been used include detachable balloons, steel (Gianturco) coils, and liquid tissue adhesives (cyanoacrylate). Often, multiple procedures are necessary before flow is significantly reduced. Gamma knife radiosurgery has been used successfully in patients with cerebral arteriovenous malformations. Surgical removal of a large fistula may be attempted in patients with severe cardiac failure and lack of improvement with medical treatment. Surgical treatment may be contraindicated or unsuccessful when the lesion is extensive and diffuse or is located in a position where adjoining tissue may be injured during the surgery or related procedures.

### 444.3 Generalized Arterial Calcification of Infancy/Idiopathic Infantile Arterial Calcification

*Robert M. Kliegman*

Generalized arterial calcification of infancy (GACI) is a rare and often lethal autosomal recessive disorder characterized by calcification of muscular arteries with fibrotic myointimal proliferation and subsequent vascular stenosis leading to tissue ischemia, poor function or infarction. Diffuse arterial calcification may begin in utero leading to hydrops fetalis; in the neonate diffuse arterial calcification leads to respiratory distress and heart failure or myocardial infarction (coronary, pulmonary arteries), hypertension (renal arteries), and poor femoral pulses (aorta, femoral arteries).

Mutations in the ectonucleotide pyrophosphatase 1 gene (*ENPP1*) are noted in 75% of patients. Serum calcium, phosphate and alkaline phosphatase levels are normal and although the vascular calcification may be seen on plain x-rays (Fig. 444-3), ultrasonography (Fig. 444-4), or CT scans may reveal calcifications not visible on plain films. A subset of patients with GACI have monoallelic or biallelic mutations in the adenosine triphosphate–binding cassette subfamily C number 6 gene (*ABCC6*), which is the gene responsible for pseudoxanthoma elasticum (PXE). PXE, an autosomal recessive disorder, is classically associated with a later onset of ectopic mineralization of elastic fibers in the skin, eyes and arteries. In addition, some surviving infants with *ENPP1* mutation develop PXE symptoms involving skin and retina (angioid streaking).

Infants with GACI have been treated with bisphosphonates with variable success. In addition, some survivors have developed hypophosphatemic rickets.
This rare autosomal recessive disorder, due to mutations in the 5' exo-nucleotidase CD73 (NT5E) results in joint and arterial (lower extremity) calcification in adults. Patients present with intermittent claudication and joint pain. Onset is probably before adulthood, as patients may be undiagnosed with nonspecific findings during adolescence.

Bibliography is available at Expert Consult.
Bibliography


Primary (essential) hypertension occurs commonly in adults and, if untreated, is a major risk factor for myocardial infarction, stroke, and renal failure. In adults with hypertension, a 5 mm Hg increase in diastolic blood pressure (BP) increased the risk of coronary artery disease by 20% and the risk of stroke by 35%. Furthermore, hypertension is implicated in the etiology of nearly 50% of adults with end-stage renal disease. The prevalence of adult hypertension increases with age, ranging from 15% in young adults to 60% in individuals older than 65 yr.

Hypertensive children, although usually asymptomatic, already manifest evidence of target organ damage. Up to 40% of hypertensive children have left ventricular hypertrophy and hypertensive children have increased carotid intima–media thickness, a marker of early atherosclerosis. Primary hypertension during childhood often tracks into adulthood. Children with BP >90th percentile have a 2.4-fold greater risk of having hypertension as adults. Similarly, nearly half of hypertensive adults had a BP >90th percentile as children. There is also an association between childhood hypertension and early atherosclerosis in young adulthood.

PREVALENCE OF HYPERTENSION IN CHILDREN

In infants and young children, systemic hypertension is uncommon, with a prevalence of <1%, but when present, it is often indicative of an underlying disease process (secondary hypertension). Severe and symptomatic hypertension in children is usually caused by secondary hypertension. In contrast, the prevalence of primary essential hypertension, mostly in older school-age children and adolescents, has increased in prevalence in parallel with the obesity epidemic. School screening studies show that approximately 10% of U.S. youth overall have prehypertension and 2.5% have hypertension. The influence of obesity on elevated BP is evident in children as young as 2-5 yr old. Approximately 20% of American youth are obese, and up to 10% of obese youth have hypertension.

DEFINITION OF HYPERTENSION

The definition of hypertension in adults is BP ≥140/90 mm Hg, regardless of body size, sex, or age. This is a functional definition that relates level of BP elevation with the likelihood of subsequent cardiovascular events. Because hypertension-associated cardiovascular events, such as myocardial infarction or stroke, usually do not occur in childhood, the definition of hypertension in children is statistical rather than functional. The National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents published the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Fourth Report) in 2004. This report established normal values based on the normative distribution of BP in healthy children and included tables with systolic and diastolic values for the 50th, 90th, 95th, and 99th percentile by age, sex, and height percentile. These normative tables can be obtained online at www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm. The Fourth Report defined hypertension as average systolic blood pressure (SBP) and/or diastolic BP that is ≥95th percentile for age, sex, and height on ≥3 occasions. Prehypertension was defined as average SBP or diastolic BP that are ≥90th percentile but <95th percentile. In adolescents beginning at age 12 yr, prehypertension is defined as BP between 120/80 mm Hg and the 95th percentile. A child with BP levels
≥95th percentile in a medical setting but normal BP outside of the office has white coat hypertension.

The Fourth Report further recommended that if BP is ≥95th percentile, then the hypertension should be staged. Children with BP between the 95th and 99th percentile plus 5 mm Hg are categorized as stage 1 hypertension, and children with BP above the 99th percentile plus 5 mm Hg have stage 2 hypertension. Stage 1 hypertension, if asymptomatic and without target organ damage, allows time for evaluation before starting treatment, whereas stage 2 hypertension calls for more prompt evaluation and pharmacologic therapy (Fig. 445-1).

MEASUREMENT OF BP IN CHILDREN

The Fourth Report and the American Heart Association recommends that children 3 yr or older should have their BP checked during every healthcare episode (the AHA recommends annual BP checks). Selected children <3 yr old should also have their BP checked, including those with a history of prematurity, congenital heart disease, renal disease, solid-organ transplant, cancer, treatment with drugs known to raise BP, other illnesses associated with hypertension (neurofibromatosis, tuberous sclerosis, others), or evidence of increased intracranial pressure.

The preferred method is by auscultation and a BP cuff appropriate for the size of the child’s arm should be used. Elevated readings should be confirmed on repeat visits before determining that a child is hypertensive. The BP should be measured with the child in the sitting position after a period of quiet for at least 5 min. Careful attention to cuff size is necessary to avoid over diagnosis, as a cuff that is too short or narrow artificially increases BP readings. A wide variety of bladder sizes should be available in any medical office where children are routinely seen. An appropriate sized cuff has an inflatable bladder that is at least 40% of the arm circumference at a point midway along the upper arm. The inflatable bladder should cover at least two thirds of the upper arm length and 80-100% of its circumference.

Systolic pressure is indicated by appearance of the 1st Korotkoff sound. Palpation is useful for rapid assessment of SBP, although the palpated pressure is generally about 10 mm Hg less than that obtained via auscultation. Oscillometric techniques are used frequently in infants and young children, but they are susceptible to artifacts and are best for measuring mean BP.

Ambulatory blood pressure monitoring (ABPM) is a procedure where the child wears a device that records BP frequently, usually every 20-30 min, throughout a 24 hr period while the child goes about usual daily activities, including sleep. This allows calculation of the mean daytime BP, sleep BP, and mean BP over 24 hr. The physician can also determine the proportion of BP measurements that are in the hypertensive range (BP load) and whether there is an appropriate decrease in BP during sleep (nocturnal dip). ABPM is particularly useful in the evaluation for white coat hypertension and may also be useful for determining risk of hypertensive target organ damage, evaluating resistance to pharmacologic therapy, and evaluating patients with hypertensive episodes on antihypertensive medication. ABPM is also useful for certain special populations such as children with chronic kidney disease, kidney transplant, and diabetes mellitus where it may provide important information on cardiovascular risk that cannot be determined as well by office measurements.

ETIOLOGY AND PATHOPHYSIOLOGY

BP is the product of cardiac output and peripheral vascular resistance. An increase in either cardiac output or peripheral resistance results in an increase in BP; if 1 of these factors increases while the other decreases, BP may not increase. When hypertension is the result of another disease process, it is referred to as secondary hypertension. When no identifiable cause can be found, it is referred to as primary (essential) hypertension. Many factors, including heredity, diet, stress, and obesity, may play a role in the development of primary hypertension. Secondary hypertension is most common in infants and younger children. The younger the child, the higher the BP and the presence of symptoms related to hypertension, the more likely there will be an underlying secondary cause of hypertension. Many childhood diseases can be responsible for chronic hypertension (Table 445-1) or acute/intermittent hypertension (Table 445-2). The most likely cause varies with age. Hypertension in the premature infant is sometimes associated with umbilical artery catheterization and renal artery thrombosis. Hypertension during early childhood may be caused by renal disease,
coarctation of the aorta, endocrine disorders, or medications. In older school-age children and adolescents, primary hypertension becomes increasingly common.

Secondary hypertension in children is most commonly caused by renal abnormalities; cardiovascular disease or endocrinopathies are additional etiologies. Renal (chronic glomerulonephritis, reflux or obstructive nephropathy, hemolytic uremic syndrome, poly cystic or dysplastic renal diseases), or renovascular hypertension, account for approximately 90% of children with secondary hypertension. Renal parenchymal disease and renal artery stenosis lead to water and sodium retention thought to be, in part, secondary to increased renin secretion. Coarctation of the aorta should always be considered. Several endocrinopathies are associated with hypertension, usually those involving the thyroid, parathyroid, and adrenal glands. Systolic hypertension and tachycardia are common in hyperthyroidism; diastolic pressure is not usually elevated. Hypercalcemia, whether secondary to hyperparathyroidism or other causes, often results in mild elevation in BP because of an increase in vascular tone. Adrenocortical disorders (aldosterone-secretting tumors, sodium retaining congenital adrenal hyperplasia, Cushing syndrome) may produce hypertension in patients with increased mineralocorticoid secretion. It is important to consider conditions associated with real or apparent mineralocorticoid excess (Table 445-3) and thus a suppressed renin level form of secondary hypertension. Pheochromocytomas are catecholamine-secreting tumors that give rise to hypertension because of the cardiac and peripheral vascular effects of epinephrine and norepinephrine. Children with pheochromocytoma usually have sustained rather than intermittent or exercise-induced hypertension. Pheochromocytoma develops in approximately 5% of patients with neurofibromatosis. Rarely, secondary hypertension can be caused by pseudo hyperaldosteronism, which leads to elevated BP in the face of a suppressed renin level. Such disorders include Liddle syndrome, apparent mineralocorticoid excess, and dexamethasone suppressible aldosteronism. Altered sympathetic tone can be responsible for acute or intermittent elevation of BP in children with Guillain-Barré syndrome, poliomyelitis, burns, and Stevens-Johnson syndrome. Symptomatic outflow from the central nervous system is also affected by intracranial lesions.

A number of drugs of abuse, therapeutic agents, and toxins may cause hypertension. Cocaine may provoke a rapid increase in BP and can

<table>
<thead>
<tr>
<th>Table 445-1</th>
<th>Conditions Associated with Chronic Hypertension in Children</th>
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<tbody>
<tr>
<td><strong>RENA L</strong></td>
<td>Chronic pyelonephritis</td>
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<td></td>
<td>Chronic glomerulonephritis</td>
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<tr>
<td></td>
<td>Hydronephrosis</td>
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<td>Congenital dysplastic kidney</td>
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<td>Multicystic kidney</td>
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<td>Solitary renal cyst</td>
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<td></td>
<td>Vesicoureteral reflux nephropathy</td>
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<td></td>
<td>Segmental hypoplasia (Ask-Upmark kidney)</td>
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<td>Ureteral obstruction</td>
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<td>Renal tumors</td>
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<td>Renal trauma</td>
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<td>Rejection damage following transplantation</td>
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<td>Postirradiation damage</td>
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<td></td>
<td>Systemic lupus erythematous (other connective tissue diseases)</td>
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<tr>
<td><strong>VASCULAR</strong></td>
<td>Coarctation of thoracic or abdominal aorta</td>
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<td></td>
<td>Renal artery lesions (stenosis, fibromuscular dysplasia, thrombosis, aneurysm)</td>
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<td></td>
<td>Umbilical artery catheterization with thrombus formation</td>
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<tr>
<td></td>
<td>Neurofibromatosis (intrinsic or extrinsic narrowing for vascular lumen)</td>
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<td>Renal vein thrombosis</td>
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<td>Vasculitis</td>
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<td>Arteriovenous shunt</td>
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<td>Williams-Beuren syndrome</td>
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<td>Moyamoya disease</td>
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<td>Takayasu arteritis</td>
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<td><strong>ENDOCRINE</strong></td>
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<td></td>
<td>Hyperparathyroidism</td>
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<td>Congenital adrenal hyperplasia (11β-hydroxylase and 17-hydroxylase defect)</td>
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<td>Cushing syndrome</td>
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<td>Primary aldosteronism</td>
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<td>Apparent mineralcorticoid excess</td>
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<td>Glucocorticoid remedial aldosteronism (familial aldosteronism type 1)</td>
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<td>Glucocorticoid resistance (Chrousos syndrome)</td>
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<td>Pseudohypoaldosteronism type 2 (Gordon syndrome)</td>
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<td>Pheochromocytoma</td>
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<td>Other neural crest tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)</td>
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<td></td>
<td>Liddle syndrome</td>
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<td>Geller syndrome</td>
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<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td>Intracranial mass</td>
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<td>Hemorrhage</td>
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<td>Residual following brain injury</td>
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<td>Quadriplegia</td>
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<tr>
<th>Table 445-2</th>
<th>Conditions Associated with Transient or Intermittent Hypertension in Children</th>
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<tr>
<td><strong>RENA L</strong></td>
<td>Acute postinfectious glomerulonephritis</td>
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<td>Anaphylactoid (Henoch-Schönlein) purpura with nephritis</td>
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<td>Hemolytic-uremic syndrome</td>
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<td></td>
<td>Acute tubular necrosis</td>
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<td>After renal transplantation (immediately and during episodes of rejection)</td>
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<td></td>
<td>After blood transfusion in patients with azotemia</td>
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<td></td>
<td>Hypervolemia</td>
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<td>After surgical procedures on the genitourinary tract</td>
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<td>Pyelonephritis</td>
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<td>Renal trauma</td>
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<td></td>
<td>Leukemic infiltration of the kidney</td>
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<td>Obstructive uropathy associated with Crohn disease</td>
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<td><strong>DRUGS AND POISONS</strong></td>
<td>Cocaine</td>
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<td>Oral contraceptives</td>
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<td>Sympathomimetic agents</td>
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<td>Amphetamines</td>
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<td>Phencyclidine</td>
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<td>Corticosteroids and adrenocorticotropic hormone</td>
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<td>Cyclosporine or sirolimus treatment posttransplantation</td>
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<td>Licorice (glycyrrhizin acid)</td>
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<td>Lead, mercury, cadmium, thallium</td>
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<td></td>
<td>Antihypertensive withdrawal (clonidine, methylpoda, propranolol)</td>
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<td>Vitamin D intoxication</td>
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<td><strong>CENTRAL AND AUTONOMIC NERVOUS SYSTEM</strong></td>
<td>Increased intracranial pressure</td>
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<td></td>
<td>Guillain-Barré syndrome</td>
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<td></td>
<td>Burns</td>
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<td>Familial dysautonomia</td>
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<td>Stevens-Johnson syndrome</td>
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<td>Posterior fossa lesions</td>
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<td>Porphyria</td>
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<td>Poliomyelitis</td>
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<td>Encephalitis</td>
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<td>Spinal cord injury (autonomic storm)</td>
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<tr>
<td><strong>MISCELLANEOUS</strong></td>
<td>Preeclampsia</td>
</tr>
<tr>
<td></td>
<td>Fractures of long bones</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>After coarctation repair</td>
</tr>
<tr>
<td></td>
<td>White cell transfusion</td>
</tr>
<tr>
<td></td>
<td>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td></td>
<td>Chronic upper airway obstruction</td>
</tr>
</tbody>
</table>

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**NOTE:**
- Conditions listed under Table 445-1 and Table 445-2 are not mutually exclusive.
result in seizures or intracranial hemorrhage. Phencyclidine causes transient hypertension that may become persistent in chronic abusers. Tobacco use may also increase BP. Sympathomimetic agents used as nasal decongestants, appetite suppressants, and stimulants for attention deficit disorder produce peripheral vasoconstriction and varying degrees of cardiac stimulation. Individuals vary in their susceptibility to these effects. Oral contraceptives should be suspected as a cause of hypertension in adolescent girls, although the incidence is lower with the use of low-estrogen preparations. Immunosuppressant agents such as cyclosporine and tacrolimus cause hypertension in organ transplant recipients, and the effect is exacerbated by the co-administration of steroids. BP may be elevated in patients with poisoning by a heavy metal.

Children and adolescents with primary (essential) hypertension are commonly overweight, often have a strong family history of hypertension, and usually have BP values at or only slightly above the 95th percentile for age. Primary hypertension is the most common form of hypertension in adults, and it is recognized more often in adolescents than in young children. The cause of primary hypertension is likely to be multifactorial; obesity, genetic alterations in calcium and sodium transport, vascular smooth muscle reactivity, the renin–angiotensin system, sympathetic nervous system overactivity, and insulin resistance have been implicated in this disorder. Elevated uric acid levels may play a role in the pathophysiology of primary hypertension and proof-of-concept studies have confirmed that lowering of uric acid levels results in lower BP in overweight youth with hypertension or prehypertension. Some children and adolescents demonstrate salt-sensitive hypertension, a factor that is ameliorated with weight loss and sodium restriction.

Normotensive children of hypertensive parents may show abnormal physiologic responses that are similar to those of their parents. When subjected to stress or competitive tasks, the offspring of hypertensive adults, as a group, respond with greater increases in heart rate and BP than do children of normotensive parents. Similarly, some children of hypertensive parents may excrete higher levels of urinary catecholamines or may respond to sodium loading with greater weight gain and increases in BP than do those without a family history of hypertension. The abnormal responses in children with affected parents tend to be greater in the black population than among white individuals.

**CLINICAL MANIFESTATIONS**

Children and adolescents with primary hypertension are usually asymptomatic; the BP elevation is usually mild and is detected during a routine examination or evaluation before athletic participation. These children may also be obese. Children with secondary hypertension can have BP elevations ranging from mild to severe. Unless the pressure has been sustained or is rising rapidly, hypertension does not usually produce symptoms. Therefore, clinical manifestations may instead reflect the underlying disease process, such as growth failure in children with chronic kidney disease. With substantial hypertension, headache, dizziness, epistaxis, anorexia, visual changes, and seizures may occur. **Hypertensive encephalopathy** (generalized or posterior reversible leukoencephalopathy syndrome) is suggested by the presence of headache, vomiting, temperature elevation, visual disturbances, ataxia, depressed level of consciousness, CT abnormalities, and seizures (Fig. 445-2). Cardiac failure, pulmonary edema, and renal dysfunction (malignant hypertension) may occur in the face of marked hypertension. Bell palsy may be seen in asymptomatic or symptomatic patients. **Hypertensive crisis** may manifest with decreased vision (retinal hemorrhages of hypertensive retinopathy) and papilledema, encephalopathy (headache, seizures, depressed level of consciousness), heart failure, or accelerated deterioration of renal function.

Subclinical hypertensive target-organ injury is a common clinical manifestation in children with essential hypertension. With the use of...
echocardiography using pediatric normative data, left ventricular hypertrophy is detected in up to 40% of hypertensive children. Other markers of target organ damage that have been demonstrated in hypertensive children include increased carotid intima–media thickness, hypertensive retinopathy, and microalbuminuria. Children with pre-hypertension also have evidence of target organ damage, often at a magnitude intermediate between that of normotensive and hypertensive children.

**DIAGNOSIS**

The evaluation of the child with chronic hypertension should be directed toward uncovering potential underlying causes of the hypertension, evaluating for comorbidities, and screening for evidence of target organ damage. The extent of the evaluation for underlying causes of hypertension depends on the type of hypertension that is suspected. When secondary hypertension is a strong consideration, as in younger children with severe and symptomatic hypertension, an extensive evaluation may be necessary (Fig. 445-3). Alternatively, overweight adolescents with a family history of hypertension who have mild elevations of BP may need only a limited number of tests.

In all cases, a careful history and physical examination are warranted. A family history for early cardiovascular events should be obtained. Growth parameters should be determined to detect evidence of chronic disease. BP should be obtained in all 4 extremities to detect coarctation (thoracic or abdominal) of the aorta. Table 445-4 identifies other features of the physical examination that may provide evidence of an underlying cause of hypertension. Unless the history and physical examination suggest another cause, children with confirmed hypertension should have an evaluation to detect renal disease, including urinalysis, electrolytes, blood urea nitrogen, creatinine, complete blood count, urine culture, and renal ultrasound. Table 445-5 provides a more complete list of tests to consider in the clinical evaluation of a child with confirmed hypertension. Measuring serum potassium is essential because hypokalemia may be present in Liddle syndrome, glucocorticoid remedial aldosteronism, and apparent mineralocorticoid excess syndrome, while hyperkalemia may be seen in Gordon syndrome.

Renovascular hypertension is often associated with other diseases (Table 445-6) but may be isolated. Magnetic resonance or CT angiography can reveal renal artery stenosis, but fluoroscopic angiography may be needed, especially to detect intrarenal arterial stenosis (Fig. 445-4).

Primary hypertension often clusters with other risk factors. All hypertensive children should be screened for comorbidities that may increase cardiovascular risk, including hyperlipidemia and glucose intolerance. A fasting lipid panel and fasting glucose level should be obtained. In addition, a sleep history should be obtained in children with confirmed hypertension to screen for sleep disordered breathing, an entity that is associated with high BP, particularly in overweight children.

Left ventricular hypertrophy (LVH) is the most common manifestation of target-organ damage in hypertensive children. All children with confirmed hypertension should have echocardiography to evaluate for the presence of LVH. Left ventricular mass measurements should be indexed to height (m²) to account for the effect of body size. The presence of LVH is an indication to treat the hypertension with pharmacologic therapy.

**PREVENTION**

Prevention of high BP may be viewed as part of the prevention of cardiovascular disease and stroke, the leading cause of death in adults in the United States. Other risk factors for cardiovascular disease include obesity, elevated serum cholesterol levels, high dietary sodium intake, and a sedentary lifestyle, as well as alcohol and tobacco use. The

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**Figure 445-4** Renal angiogram in 7 yr old boy with hypertension. Right renal artery is visible with a string-of-beads appearance characteristic of fibromuscular dysplasia (arrows). The aorta and left renal artery appear normal. (From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, Lancet 371:1453–1463, 2008, p. 1454, Fig. 1.)
Table 445-4 | Findings to Look for on Physical Examination in Patients with Hypertension

<table>
<thead>
<tr>
<th>PHYSICAL FINDINGS</th>
<th>POTENTIAL RELEVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENERAL</strong></td>
<td></td>
</tr>
<tr>
<td>Pale mucous membranes, edema, growth retardation</td>
<td>Chronic renal disease</td>
</tr>
<tr>
<td>Elfinit facies, poor growth, retardation</td>
<td>Williams syndrome</td>
</tr>
<tr>
<td>Webbing of neck, low hairline, widespread nipples, wide carrying angle</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Moon face, buffalo hump, hirsutism, truncal obesity, striae, acne</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td><strong>HABITUS</strong></td>
<td></td>
</tr>
<tr>
<td>Thinness</td>
<td>Pheochromocytoma, renal disease, hyperthyroidism</td>
</tr>
<tr>
<td>Virilization</td>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Rickets</td>
<td>Chronic renal disease</td>
</tr>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
</tr>
<tr>
<td>Cafe-au-lait spots, neurofibromas</td>
<td>Neurofibromatosis, pheochromocytoma</td>
</tr>
<tr>
<td>Tubers, “ash-leaf” spots</td>
<td>Tuberosus sclerosis</td>
</tr>
<tr>
<td>Rash</td>
<td>Systemic lupus erythematous, vasculitis (Henoeh-Schönlein purpura), impetigo with acute nephritis</td>
</tr>
<tr>
<td>Pallor, evanescent flushing, sweating</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Needle tracks</td>
<td>Illicit drug use</td>
</tr>
<tr>
<td>Bruises, striae</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Type 2 diabetes, insulin resistance</td>
</tr>
<tr>
<td><strong>EYES</strong></td>
<td></td>
</tr>
<tr>
<td>Extraocular muscle palsy</td>
<td>Nonspecific, chronic, severe</td>
</tr>
<tr>
<td>Fundal changes</td>
<td>Nonspecific, chronic, severe</td>
</tr>
<tr>
<td>Proptosis</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td><strong>HEAD AND NECK</strong></td>
<td></td>
</tr>
<tr>
<td>Goiter</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Adenotonsillar hypertrophy</td>
<td>Sleep disordered breathing</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR SIGNS</strong></td>
<td></td>
</tr>
<tr>
<td>Absent of diminished femoral pulses, low leg pressure relative to arm pressure</td>
<td>Aortic coarctation</td>
</tr>
<tr>
<td>Heart size, rate, rhythm; murmurs; respiratory difficulty, hypertomegaly</td>
<td>Aortic coarctation, congestive heart failure</td>
</tr>
<tr>
<td>Bruits over great vessels</td>
<td>Arteritis or arteriopathy</td>
</tr>
<tr>
<td>Rub</td>
<td>Pericardial effusion secondary to chronic renal disease</td>
</tr>
<tr>
<td><strong>PULMONARY SIGNS</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Congestive heart failure, acute nephritis</td>
</tr>
<tr>
<td>Picture of bronchopulmonary dysplasia</td>
<td>Bronchopulmonary dysplasia-associated hypertension</td>
</tr>
<tr>
<td><strong>ABDOMEN</strong></td>
<td></td>
</tr>
<tr>
<td>Epigastric bruit</td>
<td>Primary renovascular disease or in association with Williams syndrome, neurofibromatosis, fibromuscular dysplasia, or arteritis</td>
</tr>
<tr>
<td>Abdominal masses</td>
<td>Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidneys, hydrenephrosis, dysplastic kidneys</td>
</tr>
<tr>
<td><strong>NEUROLOGIC SIGNS</strong></td>
<td></td>
</tr>
<tr>
<td>Neurologic deficits</td>
<td>Chronic or severe acute hypertension with stroke</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Hyperaldosteronism, Liddle syndrome</td>
</tr>
<tr>
<td><strong>GENITALIA</strong></td>
<td></td>
</tr>
<tr>
<td>Ambiguous, virilized</td>
<td>Congenital adrenal hyperplasia</td>
</tr>
</tbody>
</table>

Increase in arterial wall rigidity and blood viscosity that is associated with exposure to the components of tobacco may exacerbate hypertension. Population approaches to prevention of primary hypertension include a reduction in obesity, reduced sodium intake, and an increase in physical activity through school- and community-based programs.

**TREATMENT**
The Fourth Report recommended a management algorithm for children with confirmed hypertension according to whether the child has prehypertension, stage 1 hypertension, or stage 2 hypertension (see Figs. 445-1 and 445-5). The mainstay of therapy for children with asymptomatic mild hypertension without evidence of target-organ damage is therapeutic lifestyle modification with dietary changes and regular exercise. Weight loss is the primary therapy in obesity-related hypertension. It is recommended that all hypertensive children have a diet increased in fresh fruits, fresh vegetables, fiber, and nonfat dairy, and reduced in sodium. In addition, regular aerobic physical activity for at least 30-60 min on most days along with a reduction of sedentary activities to less than 2 hr per day is recommended. Indications for pharmacologic therapy include symptoms of hypertension, secondary hypertension, hypertensive target organ damage, diabetes (types 1 and 2), and persistent hypertension despite nonpharmacologic measures (Table 445-7). When indicated, antihypertensive medication should be initiated as a single agent at low dose (see Fig. 445-5). The dose can then be increased until the goal BP is achieved. Once the highest recommended dose is reached or if the child develops side effects, then a second drug from a different class can be added. Acceptable drug classes for use in children include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics. Details on recommended doses of different
## Table 445-5  Clinical Evaluation of Confirmed Hypertension

<table>
<thead>
<tr>
<th>STUDY OR PROCEDURE</th>
<th>PURPOSE</th>
<th>TARGET POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVALUATION FOR IDENTIFIABLE CAUSES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination</td>
<td>History and physical examination help focus subsequent evaluation</td>
<td>All children with persistent BP ≥95th percentile</td>
</tr>
<tr>
<td>Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture</td>
<td>R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states</td>
<td>All children with persistent BP ≥95th percentile</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>R/O anemia, consistent with chronic renal disease</td>
<td>All children with persistent BP ≥95th percentile</td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td>R/O renal scar, congenital anomaly, or disparate renal size</td>
<td>All children with persistent BP ≥95th percentile</td>
</tr>
<tr>
<td><strong>EVALUATION FOR COMORBIDITY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid panel, fasting glucose</td>
<td>Identify hyperlipidemia, identify metabolic abnormalities</td>
<td>Overweight patients with BP at 90th-94th percentile; all patients with BP ≥95th percentile; family history of hypertension or cardiovascular disease; child with chronic renal disease</td>
</tr>
<tr>
<td>Drug screen</td>
<td>Identify substances that might cause hypertension Identify sleep disorder in association with hypertension</td>
<td>History suggestive of possible contribution by substances or drugs. History of loud, frequent snoring</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EVALUATION FOR TARGET-ORGAN DAMAGE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Identify left ventricular hypertrophy and other indications of cardiac involvement</td>
<td>Patients with comorbid risk factors* and BP 90th-94th percentile; all patients with BP ≥95th percentile</td>
</tr>
<tr>
<td>Retinal exam</td>
<td>Identify retinal vascular changes</td>
<td>Patients with comorbid risk factors and BP 90th-94th percentile; all patients with BP ≥95th percentile</td>
</tr>
<tr>
<td><strong>ADDITIONAL EVALUATION AS INDICATED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory blood pressure monitoring</td>
<td>Identify white coat hypertension, abnormal diurnal BP pattern, BP load</td>
<td>Patients in whom white coat hypertension is suspected, and when other information on BP pattern is needed</td>
</tr>
<tr>
<td>Plasma renin determination</td>
<td>Identify low renin, suggesting mineralocorticoid-related disease</td>
<td>Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension</td>
</tr>
<tr>
<td>Renovascular imaging</td>
<td>Identify renovascular disease</td>
<td>Positive family history of severe hypertension Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension</td>
</tr>
<tr>
<td>Isotopic scintigraphy (renal scan) Magnetic resonance angiography Duplex Doppler flow studies 3-Dimensional CT Arteriography: digital subtraction arteriography or classic Plasma and urine steroid levels Plasma and urine catecholamines</td>
<td>Identify steroid-mediated hypertension Identify catecholamine-mediated hypertension</td>
<td>Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension</td>
</tr>
</tbody>
</table>

R/O, rule out.

*Comorbid risk factors also include diabetes mellitus and kidney disease.


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## Table 445-6  Causes of Renovascular Hypertension in Children

<table>
<thead>
<tr>
<th>Cause</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromuscular dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syndromic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neurofibromatosis type 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tuberosus sclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Williams syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Marfan syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Takayasu disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Polyarteritis nodosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Kawasaki disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other systemic vasculitides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrinsic compression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neuroblastoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Wilms tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Umbilical artery catheterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Congenital rubella syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Transplant renal artery stenosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 445-5  Stepped-care approach to antihypertensive therapy in children and adolescents. BP, blood pressure. (From Flynn JT, Daniels SR: Pharmacologic treatment of hypertension in children and adolescents, J Pediatr 149:746–754, 2006, p. 751, Fig. 2.)

Table 445-7  Recommended Doses for Selected Antihypertensive Agents for Use in Hypertensive Children and Adolescents

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUG</th>
<th>STARTING DOSE</th>
<th>INTERVAL</th>
<th>MAXIMUM DOSE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone receptor antagonist</td>
<td>Eplerenone</td>
<td>25 mg/day</td>
<td>qd-bid</td>
<td>100 mg/day</td>
</tr>
<tr>
<td></td>
<td>Spironolactone†</td>
<td>1 mg kg⁻¹ day⁻¹</td>
<td>qd-bid</td>
<td>3.3 mg kg⁻¹ day⁻¹ up to 100 mg/day</td>
</tr>
<tr>
<td>Angiotensin- converting enzyme inhibitors</td>
<td>Benazepril†</td>
<td>0.2 mg kg⁻¹·day⁻¹ up to 10 mg/day</td>
<td>qd</td>
<td>0.6 mg kg⁻¹·day⁻¹ up to 40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Captopril†</td>
<td>0.3-0.5 mg/kg/dose</td>
<td>qid</td>
<td>6 mg kg⁻¹·day⁻¹ up to 450 mg/day</td>
</tr>
<tr>
<td></td>
<td>Enalapril†</td>
<td>0.08 mg kg⁻¹·day⁻¹</td>
<td>qd</td>
<td>0.6 mg kg⁻¹·day⁻¹ up to 40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Fosinopril</td>
<td>0.1 mg kg⁻¹·day⁻¹ up to 10 mg/day</td>
<td>qd</td>
<td>0.6 mg kg⁻¹·day⁻¹ up to 40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Lisinopril†</td>
<td>0.07 mg kg⁻¹·day⁻¹ up to 5 mg/day</td>
<td>qd</td>
<td>0.6 mg kg⁻¹·day up to 40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Quinapril</td>
<td>5-10 mg/day</td>
<td>qd</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Candesartan</td>
<td>1-6 yr, 0.2 mg kg⁻¹·day⁻¹ 6-17 yr, &lt;50 kg 4-8 mg once daily &gt;50 kg 8-16 mg qdqd</td>
<td>qd</td>
<td>1-6 yr, 0.4 mg/kg; 6-17 yr, &lt;50 kg 16 mg qd; &gt;50 kg 32 mg qd</td>
</tr>
<tr>
<td></td>
<td>Losartan†</td>
<td>0.75 mg kg⁻¹·day⁻¹ up to 50 mg/day</td>
<td>qd</td>
<td>1.4 mg kg⁻¹·day⁻¹ up to 100 mg/day</td>
</tr>
<tr>
<td></td>
<td>Olmesartan</td>
<td>20 to &lt;35 kg 10 mg qd; ≥35 kg 20 mg qd</td>
<td>qd</td>
<td>20 to &lt;35 kg 20 mg qd ≥35 kg 40 mg qd</td>
</tr>
<tr>
<td></td>
<td>Valsartan†</td>
<td>6-17 yr, 1.3 mg/kg/day up to 40 mg/day; &lt;6 yr: 5-10 mg/day</td>
<td>qd</td>
<td>6-17 yr, 2.7 mg kg⁻¹·day⁻¹ up to 160 mg/day; &lt;6 yr: 80 mg/day</td>
</tr>
<tr>
<td>α- and β-Adrenergic antagonists</td>
<td>Labetalol†</td>
<td>2-3 mg kg⁻¹·day⁻¹</td>
<td>qd-bid</td>
<td>10-12 mg kg⁻¹·day⁻¹ up to 1.2 g/day</td>
</tr>
<tr>
<td></td>
<td>Carvedilol</td>
<td>0.1 mg/kg/dose up to 12.5 mg bid</td>
<td>qd</td>
<td>0.5 mg/kg/dose up to 25 mg bid</td>
</tr>
<tr>
<td>β-adrenergic antagonists</td>
<td>Atenolol†</td>
<td>0.5-1 mg kg⁻¹·day⁻¹</td>
<td>qd-bid</td>
<td>2 mg kg⁻¹·day⁻¹ up to 100 mg/day</td>
</tr>
<tr>
<td></td>
<td>Bisoprolol/HCTZ</td>
<td>0.04 mg kg⁻¹·day⁻¹ up to 2.5/6.25 mg/day</td>
<td>qd</td>
<td>10/62.5 mg/day</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>1-2 mg kg⁻¹·day⁻¹</td>
<td>qd-bid</td>
<td>6 mg kg⁻¹·day⁻¹ up to 200 mg/day</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>1 mg kg⁻¹·day⁻¹</td>
<td>qd-bid</td>
<td>16 mg kg⁻¹·day⁻¹ up to 640 mg/day</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Amlodipine†</td>
<td>0.06 mg kg⁻¹·day⁻¹</td>
<td>qd</td>
<td>0.3 mg kg⁻¹·day⁻¹ up to 10 mg/day</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>2.5 mg/day</td>
<td>qd</td>
<td>10 mg/day</td>
</tr>
<tr>
<td></td>
<td>Isradipine†</td>
<td>0.05-0.15 mg/kg/dose</td>
<td>qd</td>
<td>0.8 mg kg⁻¹·day⁻¹ up to 20 mg/day</td>
</tr>
<tr>
<td></td>
<td>Extended-release nifedipine</td>
<td>0.25-0.5 mg kg⁻¹·day⁻¹</td>
<td>qd</td>
<td>3 mg kg⁻¹·day⁻¹ up to 120 mg/day</td>
</tr>
<tr>
<td>Central α-agonist</td>
<td>Clonidine†</td>
<td>5-10 µg/kg/day</td>
<td>bid-tid</td>
<td>25 µg/kg/day up to 0.9 mg/day</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Amiloride</td>
<td>5-10 mg/day</td>
<td>qd</td>
<td>20 mg/day</td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td>0.3 mg kg⁻¹·day⁻¹</td>
<td>qd</td>
<td>2 mg kg⁻¹·day⁻¹ up to 50 mg/day</td>
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<tr>
<td></td>
<td>Furosemide</td>
<td>0.5-2.0 mg/kg/dose</td>
<td>qd-bid</td>
<td>6 mg kg⁻¹·day⁻¹</td>
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<tr>
<td></td>
<td>HCTZ</td>
<td>0.5-1 mg kg⁻¹·day⁻¹</td>
<td>qd</td>
<td>3 mg kg⁻¹·day⁻¹ up to 50 mg/day</td>
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<tr>
<td>Vasodilators</td>
<td>Hydralazine</td>
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<td>tid-qid</td>
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<tr>
<td></td>
<td>Minoxidil</td>
<td>0.1-0.2 mg kg⁻¹·day⁻¹</td>
<td>bid-tid</td>
<td>1 mg kg⁻¹·day⁻¹ up to 50 mg/day</td>
</tr>
</tbody>
</table>

bid, Twice-daily; HCTZ, hydrochlorothiazide; qd, once daily; qid, 4 times daily; tid, 3 times daily.

*The maximum recommended adult dose should never be exceeded.
†Information on preparation of a stable extemporaneous suspension is available for these agents.

Figure 445-6 Diagnostic pathway for renovascular hypertension. (From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, Lancet 371:1453–1463, 2008, p. 1458, Fig. 6.)
classes of antihypertensive medications for children can be found in the Fourth Report available free online at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

The goal of therapy for hypertension should be to reduce BP below the 95th percentile, except in the presence of chronic kidney disease, diabetes, or target-organ damage, when the goal should be to reduce BP to less than the 90th percentile. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used for children with diabetes and microalbuminuria or proteinuric renal disease. β-Blockers or calcium channel blockers should be considered for hypertensive children with migraine headaches.

Severe, symptomatic hypertension is a hypertensive emergency that is often accompanied by cardiac failure, retinopathy, renal failure, encephalopathy, and seizures. Intravenous administration is often preferred so that the fall in BP can be carefully titrated (Table 445–8). Drug choices include labetalol, nicardipine, and sodium nitroprusside. Because too rapid a reduction in BP may interfere with adequate organ perfusion, a stepwise reduction in pressure should be planned. In general, the pressure should be reduced by 10% in the 1st hr, and 15% more in the next 3–12 hr, but not to normal during the acute phase of treatment. Hypertensive urgencies, usually accompanied by few serious symptoms such as severe headache or vomiting, can be treated either orally or intravenously. The Fourth Report also includes detailed information on antihypertensive drugs used for the management of severe hypertension in children.

Treatment of secondary hypertension must also focus on the underlying disease such as chronic renal disease, hyperthyroidism, adrenal–genital syndrome, pheochromocytoma, coartation of the aorta, or renovascular hypertension. The treatment of renovascular stenosis includes antihypertensive medications, angioplasty, or surgery (Fig. 445–6). If bilateral renovascular hypertension or renovascular disease in a solitary kidney is suspected, drugs acting on the renin-angiotensin axis are usually contraindicated because they may reduce glomerular filtration rates and produce renal failure.

Bibliography is available at Expert Consult.
Bibliography


HEMATOPOIESIS IN THE HUMAN EMBRYO AND FETUS

Hematopoiesis is the process by which the cellular elements of blood are formed. In the developing human embryo and fetus, hematopoiesis is conceptually divided into 3 anatomic stages: mesoblastic, hepatic, and myeloid. Mesoblastic hematopoiesis occurs in extraembryonic structures, principally in the yolk sac, and begins between the 10th and 14th days of gestation. By 6-8 wk of gestation the liver replaces the yolk sac as the primary site of blood cell production, and during this time the placenta also contributes as a hematopoietic site. By 10-12 wk extraembryonic hematopoiesis has essentially ceased. Hepatic hematopoiesis occurs through the remainder of gestation, although hepatic production diminishes during the second trimester while bone marrow (myeloid) hematopoiesis increases. The liver remains the predominant erythropoietic organ (few if any neutrophils are produced in the human fetal liver) through 20-24 wk of gestation.

Each hematopoietic organ houses distinct populations of cells. At 18-20 wk the fetal liver is predominantly an erythropoietic organ, while the marrow produces both erythrocytes and neutrophils. The types of leukocytes present in the fetal liver and marrow differ with gestation. Macrophages precede neutrophils in the marrow, and the ratio of macrophages to neutrophils decreases as gestation progresses. Regardless of gestational age or anatomic location, production of all hematopoietic tissues begins with pluripotent stem cells capable of both self-renewal and clonal maturation into all blood cell lineages. Progenitor cells differentiate under the influence of hematopoietic growth factors (Table 446-1). Fetal hematopoietic growth factor production is independent of maternal growth factor production (Fig. 446-1).

Erythrocytes in the fetus are larger than in adults, and at 22-23 wk gestation the mean corpuscular volume can be as high as 135 fl (Fig. 446-2, upper panel). Similarly, the mean corpuscular hemoglobin is very high at 22-23 wk, and falls relatively linearly with advancing gestation (Fig. 446-2, lower panel). In contrast, the mean corpuscular hemoglobin concentration is constant throughout gestation at 34±1 g/dL. While the size and quantity of hemoglobin in erythrocytes diminish during gestation, the hematocrit and blood hemoglobin concentration gradually increase (Fig. 446-3, upper and lower panels, respectively).

Concentrations of platelets in the blood increase gradually between 22 and 40 wk gestation (Fig. 446-4) but the platelet size, assessed by mean platelet volume, remains constant at 8±1 fl. No differences are observed between males and females in fetal and neonatal reference ranges for erythrocyte indices, hematocrit, hemoglobin, platelet counts, or mean platelet volume measurements.

FETAL GRANULOCYTOPOIESIS

Neutrophils are first observed in the human fetus about 5 wk postconception as small clusters of cells around the aorta. The fetal bone marrow space begins to develop around the 8th wk postconception, and from 8-10 wk the marrow space enlarges, but no neutrophils appear there until 10.5 wk. From 14 wk through term, the most common granulocytic cell type in the fetal bone marrow space is the neutrophil. Neutrophils and macrophages originate from a common progenitor cell but macrophages appear prior to neutrophils in the fetus, first in the yolk sac, liver, lung, and brain, all before the bone marrow cavity is formed.

Granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF) are expressed in developing fetal bone as early as 6 wk postconception and both are expressed in the fetal liver as early as 8 wk. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and stem cell factor also are distributed widely in human fetal tissues. However, no changes in expression of any of these factors, or of their specific receptors, appear to be the signal for fetal production of neutrophils or macrophages, as those signals have not yet been identified.

Fetal blood contains few neutrophils until the third trimester. At 20 wk gestation the blood neutrophil count is 0-500/mm³. Although mature neutrophils are scarce, progenitor cells with the capacity to generate neutrophil clones are abundant in fetal blood. When cultured in vitro in the presence of recombinant G-CSF, they mature into large colonies of neutrophils. The physiologic role of G-CSF includes upregulating neutrophil production, and this appears to be the case for the fetus and neonate, as well as for adults. Thus, the low quantities of circulating neutrophils the mid-trimester human fetus may be partly a result of low production of G-CSF. Monocytes isolated from the blood of adults produce G-CSF when stimulated with a variety of inflammatory mediators such as bacterial lipopolysaccharide (LPS) or interleukin (IL)-1. In contrast, monocytes isolated from the blood or organs of fetuses up to 24 wk gestation generate only small quantities of G-CSF protein and messenger RNA (mRNA) after lipopolysaccharide or IL-1 stimulation. Despite this, G-CSF receptors on the surface of neutrophils of newborn infants are equal in number and affinity to those on adult neutrophils.

In the fetus, actions of the granulocytopenic factors (G-CSF, M-CSF, GM-CSF, and stem cell factor) are not limited to hematopoiesis. Receptors for each of these are located in areas of the fetal central nervous system and gastrointestinal tract, where their patterns of expression change with development. Important developmental roles exist for these factors beyond hematopoiesis.

FETAL THROMBOPOIESIS

Platelet production occurs from 2 pools of cells: megakaryocyte progenitors and megakaryocytes. Megakaryocyte progenitors are categorized as burst-forming unit–megakaryocytes (BFU-MK), which are primitive megakaryocyte progenitors, and colony-forming unit–megakaryocytes (CFU-MK), which are more differentiated. BFU-MK produce large multifocal colonies containing ≥50 megakaryocytes, whereas CFU-MK generate smaller (3-50 cells/colony) unifocal colonies. The colonies generated by BFU-MK of fetal origin contain significantly more megakaryocytes than do those of adult origin and on that basis are thought to represent somewhat more primitive cells. Megakaryocytes are identified by their morphologic characteristics, as they undergo endoreduplication, which results in large cells with
Thrombopoietin (TPO) is the physiologic regulator of platelet production and acts as a stimulator of all stages of megakaryocyte growth and development (see Table 446-1). The gene encoding TPO is located on the long arm of chromosome 3. TPO-mRNA is expressed primarily in liver and kidney and, to a lesser extent, in marrow stroma. TPO is a primary, but not exclusive, regulator of platelet production and stimulates the proliferation and survival not only of megakaryocytic progenitors but also of erythroid, myeloid, and multipotent progenitors. Recombinant TPO supports the growth of megakaryocytic colonies of neonates and children and progenitors of preterm neonates are more sensitive to recombinant TPO than are progenitors of term neonates.

**FETAL ERYTHROPOIESIS**

Similar to hematopoietic production of other cell lines, fetal erythropoiesis is regulated by growth factors produced by the fetus, not by the mother. Erythropoietin (EPO) does not cross the human placenta. Stimulating maternal EPO production does not stimulate fetal erythropoiesis, and suppressing maternal erythropoiesis by hypertransfusion does not suppress fetal erythropoiesis.

It is unclear to what extent the mechanisms regulating erythropoiesis in adults are operative in the fetus. Of all the factors known to be involved in stimulating erythropoiesis, none plays a more central regulatory role than does EPO, a 30-39 kDa glycoprotein that binds to specific receptors on the surface of erythroid precursors and stimulates their differentiation and clonal maturation into mature erythroid cells.
EPO is produced in fetal liver during the first and second trimesters, principally by cells of monocyte/macrophage origin. After birth, the anatomic site of EPO production shifts to the kidney. The specific stimulus for this shift is unknown but may involve the increase in arterial oxygen tension that occurs at birth. Epigenetic modification of gene expression may also play a role, as it appears that renal and hepatic EPO genes are methylated to different degrees. Although EPO mRNA and protein can be found in the human fetal kidney, it is not known whether this production is biologically relevant. However, it appears that renal production of EPO is not essential for normal fetal erythropoiesis, as evidenced by the normal serum EPO concentrations and normal hematocrits of anephric fetuses.

Hemoglobins in the Fetus and Neonate

The evolutionary development of oxygen-carrying proteins, the hemoglobins, increased the ability of blood to transport oxygen. The
Hemoglobin is a complex protein consisting of iron-containing heme groups and the protein moiety globin. A dynamic interaction between heme and globin gives hemoglobin its unique properties in the reversible transport of oxygen. The hemoglobin molecule is a tetramer made up of 2 pairs of polypeptide chains, with each chain having a heme group attached. The polypeptide chains of various hemoglobins are of chemically different types. The major hemoglobin of a normal adult (HbA) is made up of 1 pair of alpha (α) and 1 pair of beta (β) polypeptide chains, represented as αβ. The major hemoglobin in the fetus (HbF), which is made up of 2 α- and 2 γ-globin chains, is represented by α2γ2.

The various globin chains differ in both the number and sequence of amino acids, and their synthesis is directed by separate genes (Fig. 446-5). Two sets of genes for the α chains are located on human chromosome 16. Two pairs of alleles provide the genetic information for the structure of the α chain. The β, γ, and δ genes are closely linked on chromosome 11.

Within the red blood cell (RBC) mass of an embryo, fetus, child, and adult, 6 different hemoglobins may normally be detected (Fig. 446-6): the embryonic hemoglobins, Gower-1, Gower-2, and Portland; the fetal hemoglobin, HbF; and the adult hemoglobins, HbA and HbA2. The electrophoretic mobilities of hemoglobins vary with their chemical structures. The time of appearance and quantitative relationships among the hemoglobins are determined by complex developmental processes.

**Embryonic Hemoglobins**

The blood of early human embryos contains 2 slowly migrating hemoglobins, Gower-1 and Gower-2, and Hb Portland, which has HbF-like mobility. The zeta (ζ) chains of Hb Portland and Gower-1 are structurally quite similar to α chains. Both Gower hemoglobins contain a unique type of polypeptide chain, the epsilon (ε) chain. Hb Gower-1 has the structure ζεε, while Gower-2 has the structure αεε. Hb Portland has the structure ζγγ. In embryos of 4–8 wk gestation, the Gower hemoglobins predominate, but by the 3rd mo they have disappeared.

**Fetal Hemoglobin**

HbF contains γ polypeptide chains in place of the β chains of HbA. Its resistance to denaturation by strong alkali is the basis for determining the presence of fetal RBCs in the maternal circulation (the Kleihauer-Betke test). After the 8th wk, HbF is the predominant hemoglobin; at 24 wk gestation it constitutes 90% of the total hemoglobin. During the 3rd trimester, a gradual decline occurs, so that at birth HbF averages 70% of the total hemoglobin. Synthesis of HbF decreases rapidly postnatally (Fig. 446-7), and by 6–12 mo of age only a trace is present. Less than 2.0% can be detected by alkali denaturation in older children and adults.
Normal Relationships Among the Hemoglobins

During fetal life and early childhood, the rates of synthesis of γ and β chains and the amounts of HbA and HbF are inversely related. This relationship has been attributed to a “switch mechanism” similar to genetic regulatory mechanisms in bacteria, but the genetic, biologic, and developmental processes that direct a switchover from predominantly γ-chain synthesis in utero to predominantly β-chain synthesis after birth are unclear. It is not certain whether the mechanisms involve selective genetic inhibition or facilitation. The increase in the α,-globin
Alterations of the Hemoglobins by Disease

Because hemoglobin containing ε-chains normally are present only very early in intrauterine life, in the past they were largely of theoretical interest. Interest has been renewed by the growing method of isolation of free fetal DNA in the maternal circulation, allowing for noninvasive fetal diagnosis of a variety of genetic traits, such as RhD (rhesus antigen D) positivity in the fetus of an RhD-negative mother. In addition, small amounts of the Gower hemoglobins (rhesus antigen D) positivity in the fetus of an RhD-negative mother. In addition, small amounts of the Gower hemoglobins have been detectable in a few newborns with trisomy 13. Increased levels of HbF may be regulated by a coordinated molecular mechanism. Differential selection and amplified production of RBC precursors derived from burst-forming unit erythroid cells result in considerable HbF production. This may be the basis for the increased levels of HbF that occur in many hypoproliferative or hemolytic anemias. Alternative explanations involve more basic epigenetic regulation through processes such as methylation and deacetylation in the DNA sequences that flank the hemoglobin gene complexes.

Figure 446-7 Pre- and postnatal changes in the percentage of total hemoglobin represented by fetal hemoglobin (HbF) (yellow). The triangles represent postnatal production by reticulocytes in premature infants, and the circles represent cord blood and postnatal reticulocyte production in term infants. (From Brown MS: Fetal and neonatal erythropoiesis. In Stockman JA, Pochedly C, editors: Developmental and neonatal hematology, New York, 1988, Raven Press.)

HbF levels may be influenced by various factors. Because the HbF level is elevated during the 1st yr of life, knowledge of its normal decline is important (see Figs. 446-6 and 446-7). In persons heterozygous for β-thalassemia (β-thalassemia trait), postpartum decrease of HbF is delayed; approximately 50% of such persons have elevated levels of HbF (>2%) in later life. In homozygous thalassemia (Cooley anemia) and in hereditary persistence of HbF, large amounts of HbF characteristically are found. In patients with major β-chain hemoglobinopathies (HbSS [hemoglobin S], HbSC [sickle cell hemoglobin C]), HbF usually is increased, particularly during childhood. Preterm infants treated with human recombinant EPO increase HbF production during active erythropoiesis. Moderate elevations of HbF may occur in many diseases accompanied by hematologic stress, such as hemolytic anemias, leukemia, and aplastic anemia, because of a minor population of RBCs that contain increased amounts of HbF. Tetramers of γ chains (γγ or Hb Barts) or β chains (ββ, HbH) may be found in α-thalassemia syndromes.

The normal adult level of HbA2 (2.0-3.4%) is seldom altered. Levels of HbA2 >3.4% are found in most persons with the β-thalassemia trait and in those with megaloblastic anemias secondary to vitamin B12 and folic acid deficiency. Decreased HbA2 levels are found in those with iron-deficiency anemia (see Chapter 455) and α-thalassemia (see Chapter 462).

**RED CELL LIFE SPAN OF THE FETUS AND NEONATE**

In general, the highest hematocrit during a person’s lifetime occurs at birth, and the lowest occurs about 10 wk later. The reasons for this rapid fall are complex, but a shortened life-span of fetal/neonatal RBC has been suggested as an important component. Specifically, the RBC life span during the fetal and neonatal period is generally thought to be considerably less than the 120-day erythrocyte life span found in normal adults. Estimates of an average 60-90 day life span were derived in the 1960s from studies of chromium (51Cr)-labeled RBC. The “extinction time” is the number of days after transfusing labeled RBC when the label is completely gone from the circulating RBC, thus it estimates the maximal RBC life span. Recent studies indicate that the extinction time of fetal/neonatal RBC is similar to that of adults. For instance, fetal RBC transfused into an ABO-compatible mother, by a fetomaternal transfusion, have an extinction time of 120 days. Moreover, erythrocytes drawn from neonates, labeled with biotin, and transfused back to the neonate, have a half-disappearance time similar to adult donor erythrocytes.

It is possible that some fraction of fetal RBC survive 120 days and are then removed in the spleen by senescence, just as occurs case in healthy adults, while other RBC are removed prematurely by an active process. Neocytolysis is one possibility explaining the active process. Neocytolysis is the active removal of young erythrocytes that were generated in relatively hypoxic conditions, following normoxic or hyperoxic conditions. Neocytolysis is the process whereby the high hematocrit of persons acclimated to high altitude falls rapidly after descent to sea level (a process somewhat analogous to the change from fetal to postbirth oxygen saturations). It will be instructive to determine whether neocytolysis is, indeed, an important regulator of erythrocyte life span and bilirubin production after birth, and whether this process explains the marked fall in hematocrit but a normal RBC “extinction time” in human neonatal physiology.

Bibliography is available at Expert Consult.
Bibliography
Anemia is defined as a reduction of the hemoglobin concentration or red blood cell (RBC) volume below the range of values occurring in healthy persons. “Normal” hemoglobin and hematocrit (packed red cell volume) vary substantially with age and sex (Table 447-1). There are also racial differences, with significantly lower hemoglobin levels in African-American children than in white non-Hispanic children of comparable age (Table 447-2). Anemia is a significant global health problem affecting children and reproductive age women (Figs. 447-1 and 447-2).

Physiologic adjustments to anemia include increased cardiac output, augmented oxygen extraction (increased arteriovenous oxygen difference), and a shunting of blood flow toward vital organs and tissues. In
addition, the concentration of 2,3-diphosphoglycerate increases within the RBC. The resultant “shift to the right” of the oxygen dissociation curve reduces the affinity of hemoglobin for oxygen and results in more complete transfer of oxygen to the tissues. The same shift in the oxygen dissociation curve can also occur at high altitude. Higher levels of erythropoietin (EPO) and consequent increased red cell production by the bone marrow further assist the body to adapt.

### HISTORY AND PHYSICAL EXAMINATION

As with any medical condition, a detailed history and thorough physical exam are essential when evaluating an anemic child. Important historical facts should include age, sex, race and ethnicity, diet, medications, chronic diseases, infections, travel, and exposures. A family history of anemia and/or associated difficulties such as splenomegaly, jaundice, or early age onset of gallstones is also of consequence. There often are few physical symptoms or signs that result solely from a low hemoglobin, particularly when the anemia develops slowly. Clinical findings generally do not become apparent until the hemoglobin level falls to <7-8 g/dL. Clinical features can include pallor, sleepiness,
irritability, and decreased exercise tolerance. Pallor can involve the tongue, nail beds, palms, or palmar creases. A flow murmur is often present. Ultimately, weakness, tachypnea, shortness of breath on exertion, tachycardia, cardiac dilation, and high-output heart failure will result from increasingly severe anemia, regardless of its cause. Unusual physical findings linked to particular underlying disease etiologies are discussed in detail in sections describing the associated disorders.

**LABORATORY STUDIES**

Initial laboratory testing should include hemoglobin, hematocrit, and red cell indices as well as a white blood cell count and differential, platelet count, reticulocyte count, and examination of the peripheral blood smear. The need for additional laboratory studies is dictated by the history, the physical, and the results of this initial testing.

**DIFFERENTIAL DIAGNOSIS**

Anemia is not a specific entity but rather can result from any of number of underlying pathologic processes. To narrow the diagnostic possibilities, anemias may be classified on the basis of their morphology and/or physiology (Fig. 447-3).

Anemias may be morphologically categorized on the basis of RBC size (mean corpuscular volume [MCV]), and microscopic appearance. They can be classified as microcytic, normocytic, or macrocytic based on whether the MCV is low, normal, or high, respectively. RBC size also changes with age, and normal developmental changes in MCV should be recognized before a designation is made (see Table 447-1). Examination of a peripheral blood smear often reveals changes in RBC appearance that will help to further narrow the diagnostic categories (Fig. 447-4). Details regarding morphologic changes associated with particular disorders are described in subsequent sections.

Anemias may also be further divided on the basis of underlying physiology. The 2 major categories are decreased production and increased destruction or loss. The 2 groups are not always mutually exclusive. Decreased RBC production may be a consequence of ineffective erythropoiesis or a complete or relative failure of erythropoiesis. Increased destruction or loss may be secondary to hemolysis, sequestration, or bleeding. The peripheral blood reticulocyte percentage or absolute number will help to make a distinction between the 2 physiologic categories. The normal reticulocyte percentage of total RBCs during most of childhood is approximately 1%, with an absolute reticulocyte count of 25,000-75,000/mm³. In the presence of anemia, EPO production and the absolute number of reticulocytes should rise. Low or normal numbers of reticulocytes generally represent an inadequate response to anemia that is associated with relative bone marrow failure or ineffective erythropoiesis. Increased numbers of reticulocytes represent a normal bone marrow response to ongoing RBC destruction (hemolysis), sequestration, or loss (bleeding).

*Figure 447-3* presents a useful approach to assessing the common causes of anemia in the pediatric age group. Children with microcytic anemia and low or normal reticulocyte counts most often have defects in erythroid maturation or ineffective erythropoiesis. Iron deficiency (see Chapter 455) is the most common cause. *Thalassemia trait* (see Chapter 462) constitutes the primary differential diagnosis when iron deficiency is suspected. Distinctions between these entities are presented in Table 455-1 (see Chapter 455). *Chronic disease or inflammation* (more often normocytic), lead poisoning, and sideroblastic anemias should also be considered and are discussed in other chapters. Microcytosis and elevated reticulocyte counts are associated with thalassemia syndromes and hemoglobins C and E (see Chapter 462). Notably, thalassemias and hemoglobinopathies are most commonly seen in patients of Mediterranean, Middle Eastern, African, or Asian descent.

![Figure 447-2](https://example.com/image1.png)

*Figure 447-2* Causes of anaemia in countries with low or middle incomes. (From Balarajan Y, Ramakrishnan U, Ozaltin E, et al: Anaemia in low-income and middle-income countries. Lancet 378:2123–2134, 2011, Fig. 2.)

![Figure 447-3](https://example.com/image2.png)

*Figure 447-3* Use of the mean corpuscular volume (MCV) and reticulocyte count in the diagnosis of anemia. (Adapted from Brunetti M, Cohen J: The Harriet Lane handbook, ed 17, Philadelphia, 2005, Elsevier Mosby, p 338.)
Normocytic anemia and low reticulocyte count characterize a large number of anemias. The anemia of chronic disease/inflammation (see Chapter 455) is usually normocytic. The anemia associated with renal failure, primarily a result of reduced EPO production, will invariably be associated with clinical and laboratory evidence of significant kidney disease. Decreased or absent red cell production secondary to transient erythroblastopenia of childhood, infection, drugs, or endocrinopathy usually results in a normocytic anemia, as does bone marrow infiltration by malignancy. In the case of invading leukemia or malignancy, abnormal leukocytes or tumor cells in association with thrombocytopenia or reduced or elevated white cell counts may be seen. Acute bleeding, hypersplenism, and congenital dyserythropoietic anemia type II (see Chapter 452) are also normocytic.

In children with normocytic anemia and an appropriate (high) reticulocyte response, the anemia is usually a consequence of bleeding, hypersplenism, or ongoing hemolysis. In hemolytic conditions, reticulocytosis, indirect hyperbilirubinemia, and increased serum lactate dehydrogenase are indicators of accelerated erythrocyte destruction. There are many causes of hemolysis, resulting from conditions that are extrinsic (usually acquired) or intrinsic (usually congenital) to the red cell. Abnormal RBC morphology (e.g., spherocytes, sickle forms, microangiopathy) identified on the peripheral smear is often helpful in ascertaining the cause.

The anemia seen in children with macrocytic blood cells is sometimes megaloblastic (see Chapter 454), resulting from impaired DNA synthesis and nuclear development. The peripheral blood smear in megaloblastic anemias contains large macroovalocytes, and the neutrophils often show nuclear hypersegmentation. The major causes of megaloblastic anemia include folate deficiency, vitamin B₁₂ deficiency, and rare inborn errors of metabolism. Other macrocytic anemias with low or normal reticulocyte counts include acquired and congenital (Diamond-Blackfan and Fanconi) aplastic anemias and hypothyroidism. Patients with trisomy 21 have macrocytic cells, although an accompanying anemia is generally not present. High MCV and reticulocytosis is seen in congenital dyserythropoietic anemias I and III, and in situations wherein hemolysis results in such a large outpouring of young red cells that the mean MCV is abnormally high.

Bibliography is available at Expert Consult.
Bibliography
Section 2
Anemias of Inadequate Production

Chapter 448
Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)
Norma B. Lerner

Diamond-Blackfan anemia (DBA) is a rare, congenital bone marrow failure syndrome that usually becomes symptomatic in early infancy. More than 90% of cases are recognized in the 1st yr of life. The disorder is characterized by anemia, usually normochromic and macrocytic, reticulocytopenia, and insufficient or absent of red blood cell (RBC) precursors in an otherwise normally cellular bone marrow. Up to 50% of affected individuals have additional, extrahematopoietic anomalies.

ETIOLOGY
DBA associated mutations were initially identified in RPS19, a gene that encodes a component protein of the small 40S ribosomal subunit. Such RPS19 mutations, all dominantly inherited, were found to be present in approximately 25% of patients. Nine other DBA genes were subsequently recognized, each encoding a different small (40S) or large (60S) ribosomal subunit protein. Mutations in 1 of the 10 ribosomal
Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)

**Epidemiology**
DBA affects about 7 individuals per 1 million live births. It is primarily an autosomal dominant disease, although other inheritance patterns may yet be demonstrated. Notably, there is substantial phenotypic diversity in DBA, even in families whose members share the same mutation, suggesting that additional genetic modifiers affect phenotypic expression of the disease. International consensus recommendations suggest that a diagnosis of “nonclassical” DBA be applied to family members harboring an established mutation or those without a known mutation but with an associated anomaly or laboratory abnormality.

**Clinical Manifestations**
Profound anemia usually becomes evident by 2-6 mo of age, occasionally somewhat later. Approximately 25% of patients are anemic at birth and hydrops fetalis occurs rarely; 92% are diagnosed within the first year of life. Approximately 50% of patients have congenital anomalies and more than 1 anomaly is found in 21% of individuals with DBA (Table 448-1). Craniofacial abnormalities are the most common (50% of patients) and include hypertelorism, snub nose, and high arched palate. Skeletal anomalies, mostly upper limb and hand, affect 30% of patients. Thumb abnormalities, including flattening of the thenar eminence and triphalangeal thumb, may be bilateral or unilateral. The radial pulse may be absent. Genitourinary (38% of patients), cardiac (30% of patients), ophthalmologic, and musculoskeletal anomalies have also been identified. Short stature is common, but it is often unclear whether this characteristic results from the disease itself, related therapies, or both.

**Laboratory Findings**
The RBCs are usually macrocytic for age, but no hypersegmented neutrophils or other characteristics of megaloblastic anemia are appreciated on the peripheral blood smear. Red cell enzyme patterns are similar to those of a “fetal” RBC population with increased expression of “i” antigen and elevated fetal hemoglobin. Erythrocyte adenosine deaminase (ADA) activity is increased in most patients with this disorder, a finding that helps distinguish congenital RBC aplasia from acquired transient erythroblastopenia of childhood (see Chapter 450). Because elevated ADA activity is not a fetal RBC feature, measurement of this enzyme may be particularly helpful when diagnosing DBA in very young infants. Thrombocytosis or, rarely, thrombocytopenia, and occasionally neutropenia, may also be present. Reticulocyte percentages are characteristically very low despite severe anemia. Bone marrow erythrocyte precursors are markedly reduced in most patients; other marrow elements are usually normal. Serum iron levels are elevated. Unlike Fanconi anemia, there is no increase in chromosomal breaks when lymphocytes are exposed to alkylating agents.

**Differential Diagnosis**
DBA must be differentiated from other anemias associated with low reticulocyte counts. The syndrome of transient erythroblastopenia of childhood (TEC) is often the primary alternative diagnosis. Table 450-1 in Chapter 450 shows a useful comparison of findings in these two disorders. TEC often is differentiated from DBA by its relatively late onset, although it occasionally develops in infants <6 mo of age (see Chapter 450). Macrocytosis, congenital anomalies, fetal red cell characteristics, and elevated erythrocyte ADA are generally associated with DBA and not with TEC.

Other inherited macrocytic bone marrow failure syndromes, particularly Fanconi anemia and Shwachman-Diamond syndrome, should also be considered in the differential as should myelodysplastic syndrome. Hemolytic disease of the newborn can also mimic features of DBA because it can have a protracted course and can be coupled with markedly reduced erythropoiesis. The anemia in this disorder usually resolves spontaneously at 5-8 wk of age. Several types of chronic hemolytic disease may be complicated by an aplastic crisis, characterized by reticulocytopenia and decreased numbers of RBC precursors. This event usually occurs after the first several mo of life and is often caused by parvovirus B19 infection (see Chapter 450). Infection with parvovirus B19 (see Chapter 251) in utero also may be associated with pure RBC aplasia in infancy, and even with hydrops fetalis at birth. When diagnosing DBA in young infants, it is important to rule out parvovirus B19 infection using the polymerase chain reaction. Other infections, including HIV, as well as drugs, immune processes, and Pearson syndrome (see Chapter 449) should also be ruled out.

Table 448-1 Range of Congenital Anomalies Observed in Diamond-Blackfan Anemia

<table>
<thead>
<tr>
<th>Craniofacial</th>
<th>Hypertelorism</th>
<th>Broad, flat nasal bridge</th>
<th>Cleft palate</th>
<th>High arched palate</th>
<th>Microcephaly</th>
<th>Micrornia</th>
<th>Microtia</th>
<th>Low-set ears</th>
<th>Low hairline</th>
<th>Epicantus</th>
<th>Ptosis</th>
</tr>
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<td>Congenital glaucoma</td>
<td>Strabismus</td>
<td>Congenital cataract</td>
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<td>Short neck</td>
<td>Webbed neck</td>
<td>Sprengel deformity</td>
<td>Klippel-Feil deformity</td>
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The list includes the anomalies that are most characteristic of DBA but is not exhaustive. Multiple anomalies, most commonly including craniofacial, are present in up to 25% of affected individuals.

TREATMENT
Corticosteroids are a mainstay of therapy, and approximately 80% of patients initially respond. Because corticosteroids impair linear growth as well as physical and neurocognitive development, many hematologists maintain infants on chronic transfusion therapy and delay the start of steroids until after age 1 yr. Prednisone or prednisolone in doses totaling 2 mg/kg/day is used as an initial trial. An increase in RBC precursors is usually seen in the bone marrow 1-3 wk after therapy is begun and is followed by peripheral reticulocytosis. The hemoglobin can reach normal levels in 4-6 wk, although the rate of response is quite variable. Once it is established that the hemoglobin concentration is increasing, the dose of corticosteroid may be reduced gradually by tapering and then by eliminating all except a single, lowest effective daily dose. This dose may then be doubled, used on alternate days, and tapered still further while maintaining the hemoglobin level at ≥9 g/dL. The target maintenance dose should not exceed 0.5 mg/kg/day or 1 mg/kg every other day. In some patients, very small amounts of prednisone, as low as 2.5 mg twice a wk, may be sufficient to sustain adequate erythropoiesis. Scheduled surveillance examinations and testing for corticosteroid side effects should be pursued in all patients, regardless of dose. Appropriate Pneumocystis prophylaxis should be used after the first month of high-dose steroids and continued until the patient is on low-dose alternate-day therapy. Many children with DBA stop taking corticosteroids, usually because of unacceptable side effects or the evolution of corticosteroid refractoriness. Only 37% of patients in the Diamond-Blackfan Anemia Registry (DBAR) (http://www.dbar.org/) remained on corticosteroids.

Patients who are nonresponders or who fail to tolerate corticosteroid therapy require transfusions at intervals of 3-5 wk to maintain a hemoglobin level greater than 8 g/dL. Some younger children may require hemoglobin levels greater than 9 g/dL in order to sustain normal growth and activities. Appropriate screening and, ultimately, the initiation of chelation therapy will be required as excess iron accumulates secondary to repeated transfusions. In one case report, a patient with DBA who was treated with L-leucine became transfusion independent and remained in remission at >5 mo.

Spontaneous remission of anemia with independence from steroid or red cell transfusion therapy has been reported. The likelihood of remission is 25% by age 25 yr, with the majority of patients experiencing remission during the first decade. Mild macrocytic anemia and increased erythrocyte ADA levels persist in these circumstances.

Hematopoietic stem cell transplantation (HSCT) can be curative. As the best outcomes occur using human leukocyte antigen (HLA)-matched sibling donors in patients 9 yr of age or younger. HLA-matched sibling HSCT is recommended in affected, transfusion dependent children between the ages of 3 and 9 yr. It is important that sibling donors be carefully screened, including genotype if known, to ensure that the donor does not carry the patient's DBA gene. Improvements in alternative donor HSCT suggests that this modality may also provide an important option for select patients.

PROGNOSIS
DBA has been identified as a cancer predisposition syndrome. The risk is increased for myelodysplastic syndrome, acute myeloid leukemia, colon carcinoma, osteogenic sarcoma, and female genital cancers. The overall actuarial survival of all patients with DBA is approximately 75% at age 40 yr, with approximately 87% for those maintained on steroids, and approximately 57% for transfusion-dependent patients. Of reported deaths, 67% were treatment related and 22% were DBA-related (malignancy and severe aplastic anemia).

Bibliography is available at Expert Consult.
Bibliography
Pearson syndrome is a rare mitochondrial disorder that presents with a hypoplastic anemia that may be initially confused with Diamond-Blackfan syndrome or transient erythroblastopenia of childhood. The marrow failure usually appears in the neonatal period and is characterized by a macrocytic anemia and, occasionally, neutropenia and thrombocytopenia. There are vacuolated erythroblasts and myeloblasts in the bone marrow. This disorder is considered a unique variant of congenital sideroblastic anemia as the marrow also contains ringed sideroblasts. The hemoglobin F level is elevated. There is multiorgan involvement manifested by failure to thrive and symptoms of exocrine pancreas dysfunction, liver and renal tubular defects, malabsorption, and myopathy. Endocrine dysfunction has also been reported. In rare cases, when the disease is not fatal in early childhood, the disorder may evolve to include symptoms consistent with Kearns-Sayre syndrome.

This disorder is caused by a mitochondrial DNA deletion of variable size and location that is similar to the mitochondrial DNA (mtDNA) deletion found in Kearns-Sayre syndrome. There is heterogeneity in different tissues and between patients, accounting for the variable clinical picture. The proportion of deleted mtDNA in the bone marrow correlates with the severity of the hematologic picture, and a change in the percentage of tissue mtDNA types over time may be associated with spontaneous improvement of red blood cell hypoproliferation. Therapy for the hematologic manifestations of the disease is primarily supportive and includes red cell transfusions to correct anemia and granulocyte colony-stimulating factor to reverse episodes of severe neutropenia.

Bibliography is available at Expert Consult.
Bibliography

Chapter 450
Acquired Pure Red Blood Cell Anemia
Norma B. Lerner

TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD

Transient erythroblastopenia of childhood (TEC) is the most common acquired red cell aplasia occurring in children. It is more prevalent than congenital hypoplastic (Diamond-Blackfan) anemia. This syndrome of severe, transient hypoplastic anemia occurs mainly in previously healthy children between 6 mo and 3 yr of age; most of the children are older than 12 mo at onset. Only 10% of affected patients are >3 yr of age. The annual incidence is estimated to be 4.3 cases per 100,000 children, although it is likely higher, because many cases might go undiagnosed and resolve spontaneously. The suppression of erythropoiesis has been linked to immunoglobulin (Ig) G, IgM, and cell-mediated mechanisms. Familial cases have been reported, suggesting
a hereditary component. TEC often follows a viral illness, although no specific virus has been consistently implicated.

The temporary suppression of erythropoiesis results in reticulocytopenia and moderate to severe normocytic anemia. Some degree of neutropenia occurs in up to 20% of cases. Platelet numbers are normal or elevated. Similar to the situation observed in iron-deficiency anemia and other red blood cell (RBC) hypoplasias, thrombocytosis is presumably caused by increased erythropoietin, which has some homology with thrombopoietin. Mean corpuscular volume (MCV) is characteristically normal for age, and fetal hemoglobin (HbF) levels are normal before the recovery phase. RBC adenosine deaminase levels are normal in this disorder, thus contrasting with the elevation noted in most cases of congenital hypoplastic anemia (Table 450-1). Differentiation from the latter disease is sometimes difficult, but differences in age at onset and in age-related MCV, HbF, and adenosine deaminase are usually helpful. The peak occurrence of TEC coincides with that of iron-deficiency anemia in infants receiving milk as their main caloric source; differences in MCV should help to distinguish between these 2 disorders.

Virtually all children recover within 1–2 mo. RBC transfusions may be necessary for severe anemia in the absence of signs of early recovery. The anemia develops slowly, and significant symptoms usually develop only with severe anemia. Corticosteroid therapy is of no value in this disorder. Any child with presumed TEC who requires >1 transfusion should be reevaluated for another possible diagnosis. In rare instances, a prolonged case of apparent TEC may be caused by parvovirus-induced RBC aplasia, occurring in children with hemolytic anemia or congenital or acquired immunodeficiencies.

**RED CELL APLASIA ASSOCIATED WITH PARVOVIRUS B19 INFECTION**

Parvovirus B19 is a common infectious agent that causes erythema infectiosum (fifth disease) (see Chapter 251). It is also the best-documented viral cause of RBC aplasia in patients with chronic hemolysis, patients who are immunocompromised, and fetuses in utero. This small, nonenveloped single-stranded virus is particularly infective and cytoytic to marrow erythroid progenitor cells, interacting specifically via binding to the red cell P antigen. In addition to decreased or absent erythroid precursors, characteristic nuclear inclusions in erythroblasts and giant pronormoblasts may be seen under the light microscope in bone marrow specimens. The virus does not cause significant anemia in immunocompetent individuals with normal red cell life spans.

**CHRONIC HEMOLYSIS**

Because parvovirus infection is usually transient, with recovery occurring in <2 wk, anemia is either not present or not appreciated in otherwise normal children whose peripheral RBC life span is 100–120 days. The RBC life span is much shorter in patients with hemolysis secondary to conditions such as hereditary spherocytosis, immune hemolytic anemia, or sickle cell disease. In these children, a brief cessation of erythropoiesis can cause severe anemia, a condition known as an aplastic crisis. When a definitive diagnosis is required, the work-up should include serum parvovirus IgM and IgG titers and, if needed, viral detection using polymerase chain reaction (PCR) techniques. Recovery from moderate to severe anemia is usually spontaneous, heralded by a wave of nucleated RBCs and subsequent reticulocytosis in the peripheral blood. A RBC transfusion may be necessary if the anemia is associated with significant symptoms.

**IMMUNODEFICIENCY**

Persistent parvovirus infection may occur in children with congenital immunodeficiency diseases, lymphoproliferative disorders, those being treated with immunosuppressive agents, and those with HIV/AIDS, because these children may be unable to mount an adequate antibody response. The resultant pure RBC aplasia may be severe, and affected children may be thought to have TEC. This type of RBC aplasia differs from TEC in that there is no spontaneous recovery and >1 transfusion is often needed. The diagnosis of parvovirus infection is made by PCR of peripheral blood or bone marrow DNA because the usual serologic responses, reflected by parvovirus serum IgM or IgG titers, are impaired in immunodeficient children. In chronically infected patients, the disease may be treated with high doses of intravenous immunoglobulin, which contains neutralizing antibody to parvovirus and is effective in the short term.

**MISCARRIAGE AND HYDROPS FETALIS**

Parvovirus infection and destruction of erythroid precursors can also occur in utero. Such events are associated with increased fetal wastage in the first and second trimesters. Infants may be born with hydrops fetalis (see Chapter 103) and anemia. The presence of persistent congenital parvovirus infection is detected by PCR of peripheral blood and/or bone marrow DNA, because immunologic tolerance to the virus can prevent the usual development of specific antibodies.

**OTHER RED CELL APLASIAS IN CHILDREN**

Acquired red cell aplasia in adults is usually mediated by a chronic antibody and often associated with disorders such as chronic lymphocytic leukemia, lymphoma, thymoma, lymphoproliferative disorders, and systemic lupus erythematosus. This chronic antibody-mediated type of RBC aplasia, often responsive to immunosuppressive therapy,
is quite rare in childhood. Cases of acquired pure red cell aplasia, attributable to T-cell suppression, have also been described.

Certain drugs, such as chloramphenicol, also can inhibit erythropoiesis in a dose-dependent manner. Reticulocytopenia, erythroid hypoplasia, and vacuolated pronormoblasts in the bone marrow are reversible effects of this drug. These effects are distinct from the idiosyncratic and rare development of severe aplastic anemia in chloramphenicol recipients. Acquired antibody-mediated pure red cell aplasia has also been found to be a rare complication in chronic kidney disease patients treated with erythropoiesis-stimulating agents. In addition to discontinuing erythropoiesis-stimulating agents therapy and addressing anemia with red cell transfusions, further treatment may include immunosuppression and renal transplantation.

Bibliography is available at Expert Consult.
Bibliography
The anemia of chronic disease (ACD), also referred to as anemia of inflammation, is found in conditions where there is ongoing immune activation. It occurs in a wide range of disorders including infections, malignancies, autoimmunity, and graft-versus-host disease. A similar anemia is associated with chronic kidney disease. ACD is typically a mild to moderate normocytic, normochromic, hypoproliferative anemia associated with a decreased serum iron and low transferrin saturation.

**ETIOLOGY**

Decreased red cell life span, impaired erythropoiesis, and an increased uptake of iron in the reticuloendothelial system are important mechanisms contributing to the anemia. The modest reduction in erythrocyte longevity is perhaps the least well understood part of the pathophysiology of ACD. Elevated levels of cytokines such as interleukin-1 may increase the macrophage’s ability to ingest and destroy erythrocytes. Defective erythropoiesis, both proliferation and differentiation of precursors, has been attributed to immune cell/cytokine-driven inhibition of erythropoietin production and suppression of the bone marrow.

ACD associated alterations in iron recycling is characterized by an accumulation of iron in reticuloendothelial macrophages despite low levels of serum iron. The diversion of iron from the circulation into the reticuloendothelial system results in functional iron deficiency, which results in the impaired heme synthesis and iron-restricted erythropoiesis that contribute to anemia. These alterations in iron metabolism have been attributed to inflammation-associated excess synthesis of hepcidin, a key regulatory protein that controls intestinal iron absorption and tissue distribution. Hepcidin, although mainly synthesized by hepatocytes, is also expressed in other cells, including monocytes and macrophages. It functions by binding to and initiating the degradation of the iron exporter, ferroportin.

**CLINICAL MANIFESTATIONS**

Although the important symptoms and signs associated with ACD are those of the underlying disease, the mild to moderate anemia can affect the patient’s quality of life.

**LABORATORY FINDINGS**

Hemoglobin concentrations are generally 6-9 g/dL. The anemia is usually normochromic and normocytic, although some patients have modest hypochromia and microcytosis, particularly if there is concomitant iron deficiency. Absolute reticulocyte counts are normal or low, and leukocytosis is common. The serum iron level is low, without the increase in serum transferrin that occurs in iron deficiency. This pattern of low serum iron and low-to-normal iron-binding protein (serum transferrin) is a regular and valuable diagnostic feature. The serum ferritin level may be elevated. The bone marrow has normal cellularity; the red blood cell precursors are decreased or adequate, marrow hemosiderin may be increased, and granulocytic hyperplasia may be present.

**TREATMENT**

The best approach to ACD is the treatment, when possible, of the underlying disorder. If the associated systemic disease can be controlled, the anemia will improve or resolve. Transfusions raise the hemoglobin concentration temporarily but are rarely indicated. Erythropoietic stimulating agents (ESAs), such as recombinant human erythropoietin (EPO) or related extended half-life formulations, increase the hemoglobin level and improve activity and the sense of well-being. When using ESAs, treatment with iron is usually necessary to produce optimal effect. Response to these agents is highly variable and poorly responsive patients may require high doses to reach target hemoglobin levels. In adults, such high doses are associated with a higher incidence of adverse events, such as stroke, cardiovascular events, cancer progression, and death, leading the FDA to require a black box warning on labels.

ACD does not respond to iron alone unless there is concomitant deficiency. Unfortunately it is a common clinical challenge to identify iron deficiency in patients with an inflammatory disease (see Chapters 447 and 455). In this circumstance, a trial of iron therapy might be helpful, although there may be no response as persistent inflammation impairs iron absorption and utilization; intravenous iron may further increase hepcidin production. Therapeutic agents that target the hepcidin–ferroportin axis are under investigation.

Bibliography is available at Expert Consult.

### 451.2 Anemia of Renal Disease

Norma B. Lerner

Anemia is common in children with chronic kidney disease (CKD). The anemia is usually normochromic, and the absolute reticulocyte count is normal or low. While most patients with end-stage renal disease (ESRD) are anemic, earlier stages of CKD are associated with a lower prevalence. In adults, lower glomerular filtration rate (GFR) has been correlated with lower hemoglobin concentration, and hemoglobin has been reported to decline below a GFR threshold of 40-60 mL/min/1.73 m². In children with CKD, hemoglobin levels decline as the GFR decreases below 43 mL/min/1.73 m².

Decreased hemoglobin values are linked to increased incidence of left ventricular hypertrophy, impaired physical activity, and a reduced quality of life in pediatric patients with CKD. In those with ESRD who are on dialysis, anemia is also associated with increased risk of hospitalization and mortality.

**ETIOLOGY**

Although the anemia of CKD shares many features with the ACD, its predominant cause is decreased EPO production by diseased kidneys. Other important causes include absolute and/or functional iron deficiency as a result of chronic blood loss (from blood sampling, surgeries, and dialysis) and disturbances in the iron metabolic pathway. Higher hepcidin levels have also been implicated in the anemia of CKD. Hepcidin is filtered by the glomerulus and excreted by the kidney; serum concentrations are increased in patients with decreased...
Bibliography


GFR. Inflammation may also be a contributing factor in pediatric dialysis patients who have elevated levels of proinflammatory cytokines. Hyperparathyroidism and deficiencies of vitamin B₁₂, folate, and carnitine may also have a role in anemia of CKD.

**LABORATORY FINDINGS**

Anemia in children with CKD is defined by age: hemoglobin (Hb) <11.0 g/dL (0.5-5 yr), <11.5 g/dL (5-12 yr), <12 g/dL (12-15 yr), <13.0 g/dL (males older than 15 yr), and <12.0 g/dL (females older than 15 yr). The anemia of CKD is hypoproliferative and usually normocytic and normochromic, unless there is concomitant iron deficiency or vitamin deficiency. The EPO level and absolute reticulocyte count are usually low. White cell and platelet counts are generally normal. Ferritin will be low if there is accompanying iron deficiency, and high if there is associated inflammation.

**TREATMENT**

Oral iron therapy is recommended for all pediatric CKD patients with anemia. Consideration of IV iron therapy may be given for those receiving maintenance hemodialysis. Oral iron at 3-6 mg of elemental iron/kg of target dry weight once daily for 3 mo and possibly IV iron if transferrin saturation (serum iron × 100/total iron-binding capacity) and/or ferritin fail to improve is recommended.

ESAs are the mainstay of therapy and, particularly for children with ESRD, these medications have greatly reduced the need for frequent transfusions, decreasing the incidence of associated iron overload and alloimmunization. It is suggested to start ESA in all children with CKD when Hb concentrations are at 9-10 g/dL, with a goal of 11-12 g/dL (some recommend 11-13 g/dL) for children on maintenance ESA therapy. Dosing varies with age and dialysis modality. Darbepoetin, a synthetic form of EPO, appears to be equally effective as recombinant human EPO and has the benefit of less-frequent dosing as a consequence of a longer half-life. Iron therapy should be continued when using ESAs as treatment demands additional iron for hemoglobin synthesis.

A subset of patients is hyporesponsive to ESAs. In the past, pediatric nephrologists often responded to EPO resistance by further escalating the dose. The increased incidence of adverse events associated with dose escalation in the adult nondialysis CKD patients has prompted some concern about this approach. Several pediatric studies have demonstrated the value of IV iron supplementation in the setting of ESA hyporesponsiveness. In the rare case in which antibody-mediated (to EPO) pure red cell aplasia develops, ESA therapy should be stopped. A study including pediatric hemodialysis patients showed a nearly 50% decrease in hepcidin levels during treatment, suggesting that for those with ESA hyporesponsiveness and iron-restricted erythropoiesis, more frequent or longer duration sessions might be of benefit.

*Bibliography is available at Expert Consult.*
Bibliography
Congenital Dyserythropoietic Anemias
Norma B. Lerner

The congenital dyserythropoietic anemias (CDAs) are a heterogeneous class of inherited disorders resulting from abnormalities of late erythropoiesis. These rare conditions are characterized by variable degrees of anemia, ineffective erythropoiesis, and secondary hemochromatosis. Dyserythropoiesis is the major cause of anemia but a shortened half-life of circulating red cells may also contribute. The CDAs have historically been classified into 3 major types (I, II, and II) based upon distinctive bone marrow morphology and clinical features, although additional subgroups and variants have also been identified.

**TYPE I CONGENITAL DYSERYTHROPOIETIC ANEMIA**

**Pathogenesis**
Type I CDA is an autosomal recessive disorder. The causative gene (CDAN1) was mapped to chromosome 15 between q15.1 and q15.3 and then successfully cloned. The gene encodes codanin-1, which is a ubiquitously expressed protein that may expedite histone assembly into chromatin and regulate the cell cycle. Although the majority of patients with bone marrow characteristics indicative of CDA1 have mutations within CDAN1, such mutations have not been detected in approximately 20% of families. Two distinctive mutations in the gene C15ORF4, predicted to encode an endonuclease, have been identified in different CDA I pedigrees.

**Clinical Manifestations**
As of 2011, there were 169 cases from 143 families recorded in the literature. Most families were from Europe and the Middle East. Although CDA I may be diagnosed at any age, most cases are recognized during childhood or adolescence. CDA I is rarely diagnosed in utero. In addition to anemia-related symptoms, other findings often include splenomegaly, jaundice, and hepatomegaly. In more severe cases, evidence of extramedullary hematopoiesis in frontal or parietal bones of the skull and in paravertebral tumors may be present. Cholelithiasis and iron overload develop over time. Type I CDA has been associated with dysmorphic features in 4-14% of cases, primarily involving the digits (syndactyly, absence of nails, supernumerary toes). Retinal angiod streaks and macular abnormalities also have been reported.

**Laboratory Findings**
Hemoglobin concentrations generally range between 7 and 11 g/dL. The anemia is usually macrocytic (mean corpuscular volume 100-120 fl), but normocytic indices may be seen during childhood. Anisopoikilocytosis is appreciated on the peripheral blood smear. In some cases, normoblasts and basophilic stippling of red blood cells (RBCs) may be seen. The reticulocyte count is inadequate for the degree of anemia. Laboratory evidence of iron overload may be present. The bone marrow aspirate shows erythroid hyperplasia, megaloblastosis, and basophilic stippling. Binucleated and, more rarely, multinucleated polychromatophilic erythroblasts are also appreciated. Incompletely divided cells with thin chromatin bridges between nuclei of pairs of erythrocytes are highly specific for type I CDA. Electron microscopy is the gold standard for diagnosis, revealing erythroblasts with a characteristic “Swiss cheese” heterochromatin pattern.

**Treatment**
Treatment of this disorder is primarily supportive. Approximately 50% of neonates with CDA I will need at least 1 red cell transfusion and some may remain transfusion dependent over subsequent years. Adolescents and adults may only require episodic transfusions during aplastic crises, infection or pregnancy. If anemia is further exacerbated by co-inherited disorders, such as thalassemia or RBC enzymopathy, the patient may become transfusion dependent. The most important long-term complication is hemosiderosis, which is caused by increased intestinal absorption of iron and ineffective erythropoiesis; consequently, transfusions should be avoided when possible to prevent further iron loading. Regular phlebotomies result in normal ferritin concentrations but if this approach is untenable oral chelation therapy should be employed when repeated ferritin levels exceed 1000 µg/L. In many cases of documented CDA type I, interferon-α has effectively raised the hemoglobin concentration, reduced splenomegaly, and reduced iron overload. Patients do not respond to erythropoietin. Splenectomy is generally not
recommended. Cholecystectomy is often required. Allogeneic bone marrow transplantation from a human-leukocyte-antigen-identical sibling has been successful in a few severe cases.

**TYPE II CONGENITAL DYSERYTHROPOIETIC ANEMIA**

**Pathogenesis**
CDA II is also an autosomal recessive disorder. Genome-wide linkage analysis identified a region of chromosome 20p11.2 as the location of the candidate CDAN2 gene that was later identified to be the SEC23B gene. This gene is known to encode the cytoplasmic coat protein (COP) II component SEC23B that is involved in endoplasmic reticulum vesicle trafficking. SEC23B gene mutations have been associated with the majority of CDA II cases.

**Clinical Manifestations**
As of 2011, there were 454 cases from 356 families with CDA II recorded, making it the most common form of CDA. Families were mostly from Europe and the Middle East. In contrast to CDA I, this diagnosis is usually made later in life, often because symptoms may be milder. Also, CDA II may be initially misdiagnosed as hereditary spherocytosis. Characteristic findings can include anemia, jaundice, splenomegaly, or hepatomegaly. Posterior mediastinal or paravertebral masses of extramedullary hematopoietic tissue may be noted and signs of iron overload may also be present.

**Laboratory Findings**
The anemia is normocytic and is generally mild. Hemoglobin levels are lower in children than adults and range between 8 and 11 g/dL. The reticulocyte count, although inadequate, may appear to be normal or increased. Anisopikilocytosis is noted and occasional basophilic stippling, as well as a few, sometimes binucleate, mature erythroblasts may be found on the peripheral smear. The bone marrow aspirate is normoblastic but hypercellular, with erythroid hyperplasia. In contrast to CDA I, there are many binucleate late polychromatic erythroblasts (10-35%) as well as a few that are multinucleate. Pseudo-Gaucher cells may be present. Electron micrographs show vesicles that are laden with endoplasmic reticulum proteins running beneath the plasma membrane. The pathognomonic finding in type II CDA is that the patient's RBCs lyse in acidified serum because of an immunoglobulin M antibody that recognizes an antigen present on CDA II cells but absent on normal cells. Type II CDA is also known by the acronym HEMPAS (hereditary erythroblastic multinuclearity with a positive acidified serum test) because it features both erythroblast multinuclearity and circulating RBCs that are sensitive to lysis by acidified normal serum. As this test is technically difficult, the diagnosis is usually made by analyzing red cell membrane proteins via sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). In CDAII there is a thinner band size and faster migration of erythrocyte anion transporter (EA1), or band 3, and band 4.5 proteins.

**Treatment**
Approximately 10% of patients will require red cell transfusions in infancy and childhood but rarely during adulthood. In contrast to type I CDA, splenectomy may provide hematologic improvement. Splenectomy does not prevent further iron overloading, even in those patients whose hemoglobin is normalized, presumably because of persistent ineffective erythropoiesis in the bone marrow. Like CDA I, secondary hemochromatosis is the most prominent long-term complication and should be approached as outlined above. Allogeneic bone marrow transplantation was successful when pursued in an adult with CDA II and β-thalassemia trait. Most patients can lead a normal life and have a normal life expectancy if complications and consequences are managed appropriately.

**TYPE III CONGENITAL DYSERYTHROPOIETIC ANEMIA**
Type III CDA is an extremely rare, ill-defined entity, manifested by a mild-to-moderate macrocytic anemia. It is inherited in an autosomal dominant fashion, although there have been cases that might represent de novo mutations or other inheritance patterns. The gene for type III CDA is KIF23, which encodes a ubiquitous protein that regulates daughter cell separation during mitosis. In contrast to other CDA types, iron overload is not clinically significant (probably because hemolysis is predominantly intravascular) and spleen size is generally normal. Patients can present with angioid streaks with macular degeneration. The blood smear shows macrocytes, anisopikilocytosis, and occasional basophilic stippling. The bone marrow is notable for giant erythroid precursors that are often multinucleated, containing up to 12 nuclei per cell. Such multinucleated erythroblasts can also be seen in myelodysplasia and erythroleukemia. Transfusions are usually not required.

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Bibliography


At birth, normal full-term infants have higher hemoglobin (Hb) levels and larger red blood cells (RBCs) than do older children and adults. However, within the 1st wk of life, a progressive decline in Hb level begins and then persists for 6–8 wk. The resulting anemia is known as the **physiologic anemia of infancy**.

With the onset of respiration at birth, considerably more oxygen becomes available for binding to Hb, and, as a consequence, the Hb–oxygen saturation increases from 50% to 95% or more. There is also a gradual, normal developmental switch from fetal to adult Hb synthesis after birth that results in the replacement of high-oxygen-affinity fetal Hb with lower-affinity adult Hb, capable of delivering more oxygen to tissues. The increase in blood oxygen content and delivery results in the downregulation of erythropoietin (EPO) production, leading to suppression of erythropoiesis. Because there is no erythropoiesis, aged RBCs that are removed from the circulation are not replaced and the Hb level decreases. The Hb concentration continues to decline until tissue oxygen needs become greater than oxygen delivery. Normally, this point is reached between 8 and 12 wk of age, when the Hb concentration is about 11 g/dL. In healthy term infants, the nadir rarely falls below 10 g/dL. At this juncture, EPO production increases and erythropoiesis resumes. The supply of stored reticuloendothelial iron, derived from previously degraded RBCs, remains sufficient for this renewed Hb synthesis, even in the absence of dietary iron intake, until approximately 20 wk of age. In all, this “anemia” should be viewed as a physiologic adaptation to extrauterine life, reflecting the excess oxygen delivery relative to tissue oxygen requirements. There is no hematologic problem, and no therapy is required unless physiologic anemia of infancy is exacerbated by other ongoing processes.

A late **hypopregenerative anemia**, with absence of reticulocytes, can occur in infants with mild hemolytic disease of the newborn. The persistence of maternally derived anti-RBC antibodies in the infant’s circulation can lead to an ongoing low-grade hemolytic anemia that can exaggerate the physiologic anemia. Lower-than-expected Hb at the “physiologic” nadir has also been seen in infants after intrauterine or neonatal RBC transfusions. When infants are transfused with adult blood containing HbA, the associated shift of the oxygen dissociation curve facilitates oxygen delivery to the tissues. Accordingly, the definition of anemia and the need for transfusion should be based not only
on the infant’s Hb level, but also on oxygen requirements and the ability of circulating RBCs to release oxygen to the tissues. Premature infants also develop a physiologic anemia, known as physiologic anemia of prematurity. The Hb decline is both more extreme and more rapid. Minimal Hb levels of 7-9 g/dL commonly are reached by 3-6 wk of age, and levels may be even lower in very small premature infants (see Chapter 103). The same physiologic factors at play in term infants are operative in preterm infants but are exaggerated. In premature infants, the physiologic Hb decline may be intensified by blood loss from repeated phlebotomies obtained to monitor ill neonates. Demands on erythropoiesis are further heightened by the premature infant’s shortened RBC life span (40-60 days) and the accelerated expansion of RBC mass that accompanies the premature baby’s rapid rate of growth. Nonetheless, plasma EPO levels are lower than would be expected for the degree of anemia, resulting in a suboptimal erythropoietic response. The reason for diminished EPO levels is not fully understood. During fetal life, EPO synthesis is handled primarily by the liver, whose oxygen sensor is relatively insensitive to hypoxia when compared to the oxygen sensor of the kidney. The developmental switch from liver to kidney EPO production is not accelerated by early birth, and thus the preterm infant must rely on the liver as the primary site for synthesis, leading to diminished responsiveness to anemia. An additional mechanism thought to contribute to diminished EPO levels may be accelerated EPO metabolism. As the pronounced decline in Hb that occurs in many very low birthweight infants is associated with abnormal clinical signs, this “anemia of prematurity” is not considered to be benign and usually requires transfusions.

Some dietary factors, such as folic acid deficiency, can aggravate physiologic anemia. Unless there has been significant blood loss, iron stores should be sufficient to maintain erythropoiesis early on. Vitamin E deficiency does not play a role in anemia of prematurity. Breast milk and infant formulas provide adequate vitamin E.

**TREATMENT**

In the full-term infant, physiologic anemia requires no therapy beyond ensuring that the infant’s diet contains essential nutrients for normal hematopoiesis. In premature infants, an optimal Hb has not been established and is usually dictated by the infant’s overall clinical condition. Transfusions may be needed to maintain the Hb at what is considered safe for that child. Premature infants who are feeding well and growing normally rarely need transfusion unless iatrogenic blood loss has been significant. Although factors such as poor weight gain, respiratory difficulties, and abnormal heart rate have prompted transfusion, the beneficial effect has not been documented. Laboratory tests such as blood lactate, EPO, and mixed venous oxygen saturation have poor predictive value. Liberal and restrictive transfusion strategies have been compared in this population. A restrictive strategy does not increase infant morbidity or mortality. In addition, long-term neurodevelopmental outcomes have been found to be poorer in liberally transfused neonates. Late exposure to packed RBC may be related to the development of necrotizing enterocolitis, and early transfusions may be associated with the risk of intraventricular hemorrhage.

When transfusions are necessary, an RBC volume of 10-15 mL/kg is recommended. It is good practice to split units derived from a single donor so that sequential transfusions can be given as required and donor exposure can be minimized. In early preterm infants (weighing <1,250 g), the half-life of transfused RBCs is about 30 days. Delayed cord clamping or umbilical cord milking at birth results in fewer transfusions and a reduction in both intraventricular hemorrhage and necrotizing enterocolitis in preterm infants. Given the impact of phlebotomy losses during monitoring in the neonatal ICU, attention to reducing unnecessary blood draws also has been advocated.

Because premature infants are known to have low plasma EPO levels, recombinant human EPO may be an alternative to transfusion for the treatment of symptomatic preterm infants with anemia of prematurity. In early studies, it was unclear whether EPO reliably reduced donor exposures and reports of adverse effects, such as a possible increase in retinopathy of prematurity, further limited a willingness to use this expensive treatment. One study of preterm infants compared the weekly use of the long-acting agent darbepoetin to triweekly EPO or placebo. Supplemental iron, folate, and vitamin E were provided and the infants were transfused according to an established protocol. Those receiving either EPO or darbepoetin received half the number of transfusions and about half the donors compared with the placebo group. The incidence of mortality, retinopathy, and intracranial hemorrhage was no different between the groups. Nonetheless, this remains an area of controversy.

_Bibliography is available at Expert Consult._
Bibliography


Megaloblastic anemia describes a group of disorders that are caused by impaired DNA synthesis. Red blood cells (RBCs) are larger than normal at every developmental stage, and there is maturational asynchrony between the nucleus and cytoplasm of erythrocytes. The delayed nuclear development becomes increasingly evident as cell divisions proceed. Myeloid and platelet precursors are also affected, and giant metamyelocytes and neutrophil bands are often present in the bone marrow. There is often an associated thrombocytopenia and leukopenia. The peripheral blood smear is notable for large, often oval, RBCs with increased mean corpuscular volume. Neutrophils are characteristically hypersegmented, with many having >5 lobes. Most cases of childhood megaloblastic anemia result from a deficiency of folic acid or vitamin B\textsubscript{12} (cobalamin), vitamins essential for DNA synthesis. Rarely, these anemias may be caused by inborn errors of metabolism. Megaloblastic anemias resulting from malnutrition are relatively uncommon in the United States, but are important worldwide (see Chapters 46 and 447).

### 454.1 Folic Acid Deficiency

Folic acid, or pteroylglutamic acid, consists of pteroic acid conjugated to glutamic acid. Biologically active folates are derived from folic acid and serve as 1-carbon donors and acceptors in many biosynthetic pathways. To form functional compounds, folates must be reduced to tetrahydrofolates in a process catalyzed by the enzyme dihydrofolate reductase. As such, they are essential for DNA replication and cellular proliferation. Like other mammals, humans cannot synthesize folate and depend on dietary sources, including green vegetables, fruits, and animal organs (e.g., liver, kidney). Folates are heat labile and water soluble; consequently, boiling or heating folate sources leads to decreased amounts of vitamin. Naturally occurring folates are in a polyglutamated form that is less efficiently absorbed than the monoglutamate species (i.e., folic acid). Dietary folate polyglutamates are hydrolyzed to simple folates that are absorbed primarily in the proximal small intestine by a specific carrier-mediated system. Folates travel in the bloodstream and are taken up in cells primarily in the form of unconjugated methyltetrahydrofolate, which is subsequently reconjugated (polyglutamated) in the cell. There is an active enterohepatic circulation. Although rare, megaloblastic anemia as a consequence of folate deficiency has its peak incidence at 4-7 mo of age, somewhat earlier than iron-deficiency anemia, although both conditions may be present concomitantly in infants with poor nutrition.
ETIOLOGY
Folic acid deficiency can occur as a consequence of inadequate folate intake, decreased folate absorption, or acquired and congenital disorders of folate metabolism or transport.

Inadequate Folate Intake
In the United States, anemia caused by insufficient folate intake usually occurs in the context of increased vitamin requirements associated with pregnancy, periods of accelerated growth, and/or chronic hemolysis. Folate requirements increase markedly during pregnancy, in part to meet fetal needs, and deficiencies are common in mothers, particularly those who are poor or malnourished. Folate supplementation is recommended from the start of pregnancy to prevent neural tube defects and to meet the needs of the developing fetus. Fortunately, folate-deficient mothers generally do not give birth to infants with clinical folate deficiency because there is selective transfer of folate to the fetus via placental folate receptors. Rapid growth after birth increases demands for folic acid and infants who are premature or ill and those with certain hemolytic disorders will have particularly high folate requirements. Human breast milk, infant formulas, and pasteurized cow's milk provide adequate amounts of folic acid. Goat's milk is deficient, and supplementation must be given when it is the child's main food. Unless supplemented, powdered milk may also be a poor source of folic acid.

Malnutrition is the most common cause of folate deficiency in older children, and those with hemoglobinopathies, infections, and/or malabsorption are at increased risk. Because body stores of folate are limited, deficiency can develop quickly in malnourished individuals. On a folate-free diet, megaloblastic anemia will occur after 2-3 mo.

Decreased Folate Absorption
Malabsorption caused by chronic diarrheal states or diffuse inflammatory disease can lead to folate deficiency. In both situations, some of the decreased folate absorption may be caused by impaired folate conjugate activity. Chronic diarrhea also interferes with the enterohepatic circulation of folate, thereby enhancing folate losses because of rapid intestinal passage. Megaloblastic anemia because of folic acid deficiency can occur in celiac disease or chronic infectious enteritis and in association with enteroenteric fistulas. Previous intestinal surgery is another potential cause of decreased folate absorption.

Certain anticonvulsant drugs (e.g., phenytoin, primidone, phenobarbital) can impair folic acid absorption, and many patients treated with these drugs have low serum levels. Frank megaloblastic anemia is rare and readily responds to folic acid therapy, even when administration of the offending drug is continued. Alcohol overuse also is associated with folate malabsorption.

Congenital Abnormalities in Folate Transport and Metabolism
Inborn errors of folate transport or metabolism are rare but can be life-threatening. Those associated with megaloblastic anemia include hereditary folate malabsorption and certain extremely uncommon enzyme deficiencies.

Hereditary folate malabsorption (HFM) is an autosomal recessive disorder that is linked to several loss-of-function mutations in the SLC46A1 gene encoding the protein-coupled folate transporter. HFM is associated with an inability to absorb folic acid, 5-tetrahydrofolate, 5-methyltetrahydrofolate, or 5-formyltetrahydrofolate (folinic acid). It can become apparent at 2-6 mo of age with megaloblastic anemia and other deficits, including infections and diarrhea. Neurologic abnormalities, attributable to folate deficiency in the central nervous system, include seizures, developmental delay, and mental retardation. Folate transport is impaired in both the intestine and at the brain's choroid plexus. Serum and cerebrospinal fluid (CSF) folate levels are very low, with a loss of the normal 3:1 ratio of CSF to serum folate.

Treatment, specifically in the context of HFM, usually involves parenteral folate, although oral administration has been useful in some cases. Reduced folates are more effective than folic acid. Folate sufficiency should be maintained in both the blood and the CSF so as to avoid important complications. The megaloblastic anemia in HFM can be reversed with relatively low levels of serum folate, but adequate CSF levels may be quite difficult to achieve, and very large folate doses may be needed.

Functional methionine synthase deficiency may result from mutations affecting the function of methionine synthase reductase or methionine synthase. These disorders are autosomal recessive and are characterized not only by megaloblastic anemia, but also by cerebral atrophy, nystagmus, blindness, and altered muscle tone. Both respond to hydroxocobalamin plus betaine with variable clinical success. Dihydrofolate reductase deficiency is extremely rare and is associated with homozygous mutations in the DHFR gene. Clinical symptoms include megaloblastic anemia and neurologic manifestations. Although methylenetetrahydrofolate (MTHFR) deficiency is the most common inborn error of folate metabolism and severe cases can produce a number of neurologic and vascular complications, there is no associated megaloblastic anemia.

Drug-Induced Abnormalities in Folate Metabolism
A number of drugs have anti-folic acid activity as their primary pharmacologic effect and regularly produce megaloblastic anemia. Methotrexate binds to dihydrofolate reductase and prevents formation of tetrahydrofolate, the active form of folate. Pyrimethamine, used in the therapy of toxoplasmosis, and trimethoprim, used for treatment of various infections, can induce folic acid deficiency and, occasionally, megaloblastic anemia. Therapy with folic acid (5-formyltetrahydrofolate) is usually beneficial.

CLINICAL MANIFESTATIONS
Besides the clinical features associated with anemia, folate-deficient infants and children may manifest irritability, chronic diarrhea, and/or poor weight gain. Hemorrhages from thrombocytopenia may occur in advanced cases. Congenital folate malabsorption and other rare etiologies of folate deficiency may be further associated with hypogammaglobulinemia, severe infections, failure to thrive, neurologic abnormalities, and cognitive delays.

LABORATORY FINDINGS
The anemia is macrocytic (mean corpuscular volume >100 fL). Variations in RBC shape and size are common (see Fig. 447-4B in Chapter 447). The reticulocyte count is low, and nucleated RBCs with megaloblastic morphology are often seen in the peripheral blood. Neutropenia and thrombocytopenia may be present, particularly in patients with long-standing and severe deficiencies. The neutrophils are large, some with hypersegmented nuclei. The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation are also seen.

Normal serum folic acid levels are 5-20 ng/mL; with deficiency, levels are <3 ng/mL. Levels of RBC folate are a better indicator of chronic deficiency. The normal RBC folate level is 150-600 ng/mL of packed cells. Levels of iron and vitamin B12 in serum usually are normal or elevated. Serum activity of lactate dehydrogenase, a marker of ineffective erythropoiesis, is markedly elevated.

TREATMENT
When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. If the specific diagnosis is in doubt, smaller doses of folate (0.1 mg/day) may be used for 1 wk as a diagnostic test, because a hematologic response can be expected within 72 hr. Doses of folate >0.1 mg can correct the anemia of vitamin B12 deficiency but might aggravate any associated neurologic abnormalities. In most medical settings in developed countries, this therapeutic trial to distinguish the different causes of megaloblastic anemia is rarely necessary because vitamin B12 and folate blood levels are usually readily available. Folic acid therapy (0.5-1.0 mg/day) should be continued for 3-4 wk until a definite hematologic response has occurred. Maintenance therapy with a multivitamin (containing 0.2 mg of folate) is adequate. As described above, very high doses of
folic acid may be required in the setting of HFM. Transfusions are indicated only when the anemia is severe or the child is very ill.

Bibliography is available at Expert Consult.

454.2 Vitamin B₁₂ (Cobalamin) Deficiency
Norma B. Lerner

Vitamin B₁₂, a generic term encompassing all biologically active cobalamin, is a water-soluble vitamin with a central, functional cobalt atom and a planar corrin ring. Dicyclocobalamin and azidesocobalamin are the metabolically active derivatives, serving as cofactors in 2 essential metabolic reactions, namely methylation of homocysteine to methionine (via methionine synthase) and conversion of methyl-malonyl-coenzyme A (CoA) to succinyl CoA (via 1-methyl-malonyl-CoA mutase). The products and by-products of these enzymatic reactions are critical to DNA, RNA, and protein synthesis.

Cobalamin is synthesized exclusively by microorganisms and humans must rely on dietary sources (animal products including meat, eggs, fish, and milk) for their needs. Unlike folate, older children and adults have sufficient vitamin B₁₂ stores to last 3-5 yr. In young infants born to mothers with low vitamin B₁₂ stores, clinical signs of cobalamin deficiency can become apparent in the first 6-18 mo of life.

METABOLISM
Under normal circumstances, cobalamin is released from food protein in the stomach via peptic digestion. Cobalamin then binds to haptocorrin (HC), a salivary glycoprotein. This complex moves into the duodenum, where HC is digested by pancreatic proteases and cobalamin is liberated. Cobalamin then binds to intrinsic factor (IF), another glycoprotein that is produced by gastric parietal cells. The cobalamin-IF complex subsequently enters mucosal cells of the distal ileum by receptor-mediated endocytosis. The IF-cobalamin receptors are composed of a complex of 2 proteins, cubilin (CUBN) and amnionless (AMN), collectively known as cubam. Following internalization into enterocytes, IF is degraded in the lysosome and cobalamin is released. The transporter ABCC1 (also known as MRP1) exports cobalamin bound to the transport protein transcobalamin (TC), out of the cell. In the bloodstream, cobalamin is associated with either TC (approximately 20%) or HC. TC mediates B₁₂ transport across cells after complexing with the TC receptor, which is internalized in the lysosome. Lysosomal degradation of TC releases cobalamin which remains in the cell where it is further processed. Two distinct membrane proteins transport cobalamin across the lysosomal membrane into the cytoplasm. There, cobalamins are processed to a common intermediate that can be allocated to the methylcobalamin and adenosylcobalamin synthesis pathways to meet cellular needs. It is postulated that the MMACHC protein, a product of the cobalamin (Cbl) C locus, accepts the cobalamins exiting the lysosome. A definitive role for HC is yet to be established, but it has been suggested that it plays a role in B₁₂ storage.

ETIOLOGY
Vitamin B₁₂ deficiency can result from inadequate dietary intake of Cbl, lack of IF, impaired intestinal absorption of IF-Cbl, or absence of vitamin B₁₂ transport protein.

Inadequate Vitamin B₁₂ Intake
B₁₂ deficiency in infants is most often nutritional, resulting from low B₁₂ levels in the breast milk of B₁₂-deficient mothers. Associated megaloblastic anemia often appears during the 1st yr of life. Maternal deficiency may be caused by pernicious anemia or gastrointestinal disorders such as Helicobacter pylori infection, celiac disease, Crohn disease, or pancreatic insufficiency. Previous gastric bypass surgery, treatment with proton pump inhibitors, or inadequate intake from a strict vegetarian diet has also been implicated. Fortunately, as a result of active placental Cbl transport in utero, most children of deficient mothers maintain Cbl levels sufficient to support adequate prenatal development. Such infants are born with low stores, the depletion of which is associated with a gradual onset of clinical manifestations. B₁₂ replacement often results in rapid improvement, but the longer the deficient period, the greater the likelihood of permanent disabilities. Neonatal screening programs may detect maternal–neonatal nutritional B₁₂ deficiency as a result of an increase in propionyl carnitine, but there is higher sensitivity using a measurement of methylmalonic acid. In high-income countries, dietary deficiency during childhood or adolescence is infrequent but can result, as in adults, from strict vegetarian or vegan diet. Daily requirements range from 0.4-2.4 μg.

Impaired Absorption
Gastric surgery or medications that impair gastric acid secretion may result in IF deficiency, leading to decreased vitamin B₁₂ absorption. Pancreatic insufficiency can also lead to Cbl deficiency as a consequence of impaired cleavage and IF complex formation. Patients with neonatal necrotizing enterocolitis, inflammatory bowel disease, celiac disease, or surgical removal of the terminal ileum, may also have impaired absorption of vitamin B₁₂. An overgrowth of intestinal bacteria with diverticula or duplications of the small intestine can cause vitamin B₁₂ deficiency by consumption of (or competition for) the vitamin or by splitting of its complex with IF. In these cases, hematologic response can follow appropriate antibiotic therapy. In endemic areas, when the fish tapeworm Diphyllobothrium latum infests the upper small intestine, similar mechanisms may be operative. When megaloblastic anemia occurs in such situations, the serum vitamin B₁₂ level is low and the gastric fluid contains IF.

Hereditary intrinsic factor deficiency (HIFD) is a rare autosomal recessive disorder caused by a variety of mutations in the IF gene that produce a lack of gastric IF or a functionally abnormal IF. It differs from typical adult pernicious anemia in that gastric acid is secreted normally and the stomach is histologically normal. It is not associated with antibodies or endocrine abnormalities. Unlike Imerslund-Grasbeck syndrome (described below), hereditary IF deficiency is only occasionally associated with proteinuria. Symptoms become prominent at an early age (6-24 mo), consistent with exhaustion of vitamin B₁₂ stores acquired in utero. As the anemia becomes severe, weakness, irritability, anorexia, and listlessness occur. The tongue is smooth, red, and painful. Neuropathologic manifestations include axatia, paresthesias, hyporeflexia, Babinski responses, and clonus. Oral vitamin B₁₂ is usually ineffective and lifelong parenteral (IM) Cbl should be used to bypass the absorption defect. The natural form, hydroxocobalamin (OHcBl) is believed to be more effective than the synthetic form, cyanocobalamin (CNCbl). In one retrospective study involving patients with HIFD and Imerslund-Grasbeck syndrome, patients with acute and severe anemia were initially treated with 1 mg of IM OHcBl daily until reticulocyte recovery after which dosing was spaced to once a week. Those without severe anemia were treated with weekly IM OHcBl or CNCbl. With cautious monitoring, all patients were ultimately safely maintained on a schedule of 1 mg of IM OHcBl or CNCbl every 6 mo.

Imerslund-Grasbeck syndrome is a rare, recessively inherited pediatri c disorder resulting in selective vitamin B₁₂ malabsorption in the ileum, and consequent vitamin B₁₂ deficiency. It usually becomes clinically apparent within the first 6 yr of life. In addition to megaloblastic anemia, the patient may also have neurologic defects (such as hypotonia, developmental delay, brain atrophy, movement disorders, and dementia) and/or proteinuria. Patients carry mutations in either CUBN or AMN, proteins that form the cubam receptor for the ileal IF-Cbl complex. Because CUBN is also a key receptor for protein reabsorption in the kidney, impaired expression at this site results in associated proteinuria. The disease can be fatal if it remains untreated. Early diagnosis and treatment with IM Cbl (see treatment for HIFD above) will reverse the hematologic and neurologic abnormalities. Proteinuria does not respond to therapy.

Classic pernicious anemia (autoimmune gastritis) usually occurs in older adults but can rarely affect children. This disorder (juvenile pernicious anemia) usually presents during adolescence. In such cases,
Bibliography

the disease is associated with various detectable antibodies, including those against IF and the hydrogen potassium adenosine triphosphatase proton pump in gastric parietal cells. These children can have additional immunologic abnormalities, cutaneous candidiasis, hypoparathyroidism, and other endocrine deficiencies. There may be atrophy of the gastric mucosa and achlorhydria. Parenteral vitamin B₁₂ should be administered regularly.

**Absence of Vitamin B₁₂ Transport Protein**
TC deficiency is a rare cause of megaloblastic anemia. A congenital deficiency is inherited as an autosomal recessive condition resulting in a failure to absorb and transport vitamin B₁₂. Most patients lack TC but some have functionally defective forms. This disorder usually manifests in the first weeks of life. Characteristically, there is failure to thrive, diarrhea, vomiting, glossitis, neurologic abnormalities, and megaloblastic anemia. The diagnosis can be difficult given that total serum vitamin B₁₂ levels are often normal because approximately 80% of serum Cbl is bound to HC. The diagnosis is suggested by the presence of severe megaloblastic anemia in the face of normal folate levels and no evidence of any other inborn errors of metabolism. Plasma homocysteine and/or methylmalonic acid levels are elevated. A definitive diagnosis is made by measuring plasma TC. The serum vitamin B₁₂ levels must be kept high in order to force enough Cbl into cells to allow normal function. Oral Cbl (CNCbl or OHCbl) 500-1000 µg twice a wk, or IM OHCbl 1,000 µg per wk, may be used for initial therapy. Symptoms and laboratory studies should be monitored and doses adjusted as needed.

**Inborn Errors of Cobalamin Metabolism**
The conversion of Cbl to methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl) involves a number of steps, abnormalities of which have been tied to several distinct alphabetically labeled disorders. In CblE and CblG, defective N5-methyltetrahydrofolate-homocysteine methyltransferase fails to produce MeCbl. Patients present in infancy with megaloblastic anemia, vomiting, and mental retardation, and are found to have homocystinuria and hyperhomocysteinemia. They do not have methylmalonic aciduria or methylmalonic acidemia. They show good response to CNCbl. AdoCbl and MeCbl are both affected by CblC (the most common of the Cbl inborn errors), CblD, and CblF. Patients can present in early infancy through adolescence. Newborns have lethargy, failure to thrive, and neurologic problems. Older patients may present with neurologic difficulties, dementia, and psychological problems. Megaloblastic anemia occurs in about half the cases. Patients have elevations of homocysteine and methylmalonic acid in both urine and blood. Affected individuals respond partially to OHCbl or CNCbl. CblA, CblB, and CblH are associated with methylmalonic aciduria and a variety of serious symptoms, but megaloblastic anemia is absent.

**CLINICAL MANIFESTATIONS**
Children with Cbl deficiency often present with nonspecific manifestations such as weakness, lethargy, feeding difficulties, failure to thrive, and irritability. Other common findings include pallor, glossitis, vomiting, diarrhea, and icterus. Neurologic symptoms can include parasthesia, sensory deficits, hypotonia, seizures, developmental delay, developmental regression, and neuropsychiatric changes. Neurologic problems from vitamin B₁₂ deficiency may occur in the absence of any hematologic abnormalities.

**LABORATORY FINDINGS**
The hematologic manifestations of folate and Cbl deficiency are identical. The anemia resulting from Cbl deficiency is macrocytic, with prominent macro-ovalocytosis of the RBCs (see Fig. 447-2 in Chapter 447). The neutrophils may be large and hypersegmented. In advanced cases, neutropenia and thrombocytopenia can occur, simulating aplastic anemia or leukemia. Serum vitamin B₁₂ levels are low, and the serum concentrations of methylmalonic acid and homocysteine are usually elevated. Concentrations of serum iron and serum folic acid are normal or elevated. Serum lactate dehydrogenase activity is markedly increased, a reflection of ineffective erythropoiesis. Moderate elevations of serum bilirubin levels (2-3 mg/dL) also may be found. Excessive excretion of methylmalonic acid in the urine (normal, 0-3.5 mg/24 hr) is a reliable and sensitive index of vitamin B₁₂ deficiency.

**DIAGNOSIS**
A comprehensive medical history is essential to the clinical recognition of possible Cbl deficiency. Information regarding clinical symptoms, dietary history, diseases, surgeries, or medications is likely to provide important clues. The physical exam may reveal relevant findings such as irritability, pallor, or specific neurologic symptoms. Screening laboratory findings (described above) offer important information but more focused testing will be required to confirm a diagnosis of vitamin B₁₂ deficiency and its cause. Cbl deficiency is usually identified by measuring total or TC bound vitamin B₁₂ in the blood. Although an extremely low level is generally diagnostic, this may not be the case, and false negatives and positives are reportedly common using currently available assays. As a result, it is wise not to discount vitamin B deficiency, particularly in the face of clinical symptoms, macrocytic anemia, an abnormal blood smear, and a normal folate level. In nontreated patients, methylmalonic acid and total homocysteine levels are often helpful as they are markedly elevated in the majority of those with clinical signs of B₁₂ deficiency. Excessive excretion of methylmalonic acid in the urine (normal: 0-3.5 mg/24 hr) is also a sensitive index of vitamin B₁₂ deficiency. Although modest increases occur with renal failure, elevated methylmalonic acid is otherwise quite specific for vitamin B₁₂ deficiency. Notably, however, serum homocysteine is also elevated in folate deficiency, homocystinuria, and renal failure. If B₁₂ deficiency has been confirmed and there is no evidence of inadequate dietary intake or, in the case of an infant, inadequate maternal B₁₂, malabsorption should be investigated. In the past, the Schilling test, a measure of Cbl absorption, was the gold standard. The test is no longer available and there is currently no comparable replacement for it. Anti–IF antibodies and anti–parietal cell antibodies are useful for the diagnosis of pernicious anemia. Measurement of IF and help from more specialized laboratories may be required for less common disorders.

**TREATMENT**
Treatment regimens in children have not been well studied. The cause of vitamin B₁₂ deficiency should ultimately dictate treatment dosage as well as the duration of therapy. Dose adjustments should be made in response to clinical status and laboratory values. The physiologic requirement for vitamin B₁₂ is about 1-3 µg/day. Hematologic responses have been observed with small doses, indicating that administration of a minidose may be used as a therapeutic test when the diagnosis of vitamin B₁₂ deficiency is in doubt or in circumstances where the anemia is severe and higher initial doses might result in severe metabolic disturbances.

Bibliography is available at Expert Consult.

**454.3 Other Rare Megaloblastic Anemias**
Norma B. Lerner

Orotic aciduria is a rare autosomal recessive disorder that usually appears in the 1st yr of life and is characterized by growth failure, developmental retardation, megaloblastic anemia, and increased urinary excretion of orotic acid (see Chapter 89). This defect is the most common metabolic error in the de novo synthesis of pyrimidines and therefore affects nucleic acid synthesis. The usual form of hereditary orotic aciduria is caused by a deficiency (in all body tissues) of orotidine phosphoribosyl transferase and orotidine-5-phosphate decarboxylase. 2 sequential enzymatic steps in pyrimidine nucleotide synthesis. The diagnosis is suggested by the presence of severe megaloblastic anemia with normal serum B₁₂ and folate levels and no evidence of TC deficiency. A presumptive diagnosis is made by finding increased urinary orotic acid. However, confirmation of the diagnosis requires assay of the transferase and decarboxylase enzymes in the patient's
Bibliography
erythrocytes. Physical and mental retardation often accompany this condition. The anemia is refractory to vitamin B\textsubscript{12} or folic acid, but responds promptly to administration of uridine.

**Thiamine-responsive megaloblastic anemia** (Rogers syndrome) is a very rare autosomal recessive disorder characterized by megaloblastic anemia, sensorineural deafness, and diabetes mellitus. Congenital heart defects, arrhythmias, visual problems, short stature, tri-lineage myelodysplasia, and strokes are also described. Thiamine-responsive megaloblastic anemia usually presents in infancy but may occasionally develop in childhood and adolescence and occurs in several ethnically distinct populations. The bone marrow is characterized not only by megaloblastic changes but also by ringed sideroblasts. The defect is caused by mutations in the \textit{SCL19A2} gene on chromosome 1, which encodes a high-affinity plasma membrane thiamine transporter. Continuous thiamine supplementation usually reverses the anemia and diabetes but not existing hearing defects.

\textit{Bibliography is available at Expert Consult.}
**Bibliography**
Iron deficiency is the most widespread and common nutritional disorder in the world. It is estimated that 30% of the global population has iron-deficiency anemia, and most of them live in developing countries. In the United States, 9% of children ages 12-36 mo are iron deficient, and 30% of this group progresses to iron-deficiency anemia.

A full-term newborn infant contains about 0.5 g of iron, compared to 5 g of iron in adults. This change in quantity of iron from birth to adulthood means that an average of 0.8 mg of iron must be absorbed each day during the first 15 yr of life. A small additional amount is necessary to balance normal losses of iron by shedding of cells. It is therefore necessary to absorb approximately 1 mg daily to maintain positive iron balance in childhood. Because <10% of dietary iron usually is absorbed, a dietary intake of 8-10 mg of iron daily is necessary to maintain iron levels. During infancy, when growth is most rapid, the approximately 1 mg/L of iron in cow’s and breast milk makes it difficult to maintain body iron. Breastfed infants have an advantage because they absorb iron 2-3 times more efficiently than infants fed cow’s milk.

ETIOLOGY

Most iron in neonates is in circulating hemoglobin. As the relatively high hemoglobin concentration of the newborn infant falls during the first 2-3 mo of life, considerable iron is recycled. These iron stores are usually sufficient for blood formation in the first 6-9 mo of life in term infants. Stores are depleted sooner in low-birthweight infants or infants with perinatal blood loss because their iron stores are smaller. Delayed (1-3 min) clamping of the umbilical cord can improve iron status and reduce the risk of iron deficiency, whereas early clamping (<30 sec) puts the infant at risk for iron deficiency. Dietary sources of iron are especially important in these infants. In term infants, anemia caused solely by inadequate dietary iron usually occurs at 9-24 mo of age and is relatively uncommon thereafter. The usual dietary pattern observed in infants and toddlers with nutritional iron-deficiency anemia in developed countries is excessive consumption of cow’s milk (low iron content, blood loss from milk protein colitis) in a child who is often overweight. Worldwide, undernutrition is usually responsible for iron deficiency.

Blood loss must be considered as a possible cause in every case of iron-deficiency anemia, particularly in older children and adolescents.

Chronic iron-deficiency anemia from occult bleeding may be caused by a lesion of the gastrointestinal (GI) tract, such as peptic ulcer, Meckel diverticulum, polyp, hemangioma, or inflammatory bowel disease. Infants can have chronic intestinal blood loss induced by exposure to whole cow’s milk protein. This GI reaction is not related to enzymatic abnormalities in the mucosa, such as lactase deficiency, or to an immunoglobulin E-associated milk allergy. Involved infants characteristically develop anemia that is more severe and occurs earlier than would be expected simply from an inadequate intake of iron. The ongoing loss of blood in the stools can be prevented either by breastfeeding or by delaying the introduction of whole cow’s milk in the 1st yr of life and then limiting the quantity to <24 oz/24 hr. Unrecognized blood loss also can be associated with chronic diarrhea and, rarely, with pulmonary hemosiderosis. In developing countries, infections with hookworm, Trichuris trichiura, Plasmodium, and Helicobacter pylori often contribute to iron deficiency. Celiac disease and giardiasis may interfere with iron absorption.

Approximately 2% of adolescent girls have iron-deficiency anemia, largely as a result of their adolescent growth spurt and menstrual blood loss. The highest risk of iron-deficiency anemia (>30%) is among teenagers who are or have been pregnant.

CLINICAL MANIFESTATIONS

Most children with iron deficiency are asymptomatic and are identified by recommended laboratory screening at 12 mo of age, or sooner if at high risk. Pallor is the most important clinical sign of iron deficiency but is not usually visible until the hemoglobin falls to 7-8 g/dL. It is most readily noted as pallor of the palms, palmar creases, nail beds, or conjunctivae. Parents often fail to note the pallor because of the typical slow decline of hemoglobin over time. Often a visiting friend or relative is the first to notice. In mild to moderate iron deficiency (i.e., hemoglobin levels of 6-10 g/dL), compensatory mechanisms, including increased levels of 2,3-diphosphoglycerate and a shift of the oxygen dissociation curve, may be so effective that few symptoms of anemia aside from mild irritability are noted. When the hemoglobin level falls to <5 g/dL, irritability, anorexia, and lethargy develop, and systolic flow murmurs are often heard. As the hemoglobin continues to fall, tachycardia and high output cardiac failure can occur.

Iron deficiency has nonhematologic systemic effects. Both iron deficiency and iron-deficiency anemia are associated with impaired neurocognitive function in infancy. There is also an association of iron-deficiency anemia and later, possibly irreversible, cognitive defects. Although there is support for iron deficiency with or without anemia causing these defects, it has not been established unequivocally. Some studies suggest an increased risk of seizures, strokes, breathholding spells in children, and exacerbations of restless leg syndrome in adults. Given the frequency of iron deficiency and iron-deficiency anemia and the potential for adverse neurodevelopmental outcomes, minimizing the incidence of iron deficiency is an important goal.

Other nonhematologic consequences of iron deficiency include pica, the desire to ingest nonnutritive substances, and pagophagia, the desire to ingest ice. The pica can result in the ingestion of lead-containing substances and result in concomitant plumblism (see Chapter 721).

LABORATORY FINDINGS

In progressive iron deficiency, a sequence of biochemical and hematologic events occurs (Tables 455-1 and 455-2). First, tissue iron stores are depleted. This depletion is reflected by reduced serum ferritin, an iron-storage protein, which provides an estimate of body iron stores in the absence of inflammatory disease. Next, serum iron levels decrease, the iron-binding capacity of the serum (serum transferrin) increases, and the transferrin saturation falls below normal. As iron stores decrease, iron becomes unavailable to complex with protoporphyrin to form heme. Free erythrocyte protoporphyrins accumulate, and hemoglobin synthesis is impaired. At this point, iron deficiency progresses to iron-deficiency anemia. With less available hemoglobin in each cell, the red cells become smaller and varied in size. The variation in red cell size is measured by an increasing red cell distribution width. This is followed by a decrease in mean corpuscular volume and mean corpuscular hemoglobin. Developmental changes in mean corpuscular
Table 455-1  Indicators of Iron-Deficiency Anemia

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>SELECTED CUTOFF VALUES TO DEFINE IRON DEFICIENCY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&lt;11.0 for non-Hispanic whites ages 0.5-4 yr</td>
<td>When used alone, it has low specificity and sensitivity. Use appropriate age specific normal values found in Table 447-1. Normal values for African-Americans are found in Table 447-2.</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV) (µm³)</td>
<td>&lt;70 from 6-24 months</td>
<td>A reliable, but late indicator of iron deficiency (ID). Low values can also be a result of thalassemia and other causes of microcytosis. Normal values are found in Table 447-1.</td>
</tr>
<tr>
<td>Serum ferritin (SF) (µg/L)</td>
<td>≤5 yr &lt;12 Children &gt;5 yr &lt;15 In all age groups in the presence of infection &lt;30</td>
<td>It is probably the most useful laboratory measure of iron stores and helps identify ID; a low value of SF is diagnostic of iron-deficiency anemia (IDA) in a patient with anemia. SF is an acute phase reactant that increases in many acute or chronic inflammatory conditions independent of iron status. Combining SF with a measurement of C-reactive protein (CRP) helps to identify these false-negative SF results.</td>
</tr>
<tr>
<td>Reticulocyte hemoglobin content (CHr) (pg)</td>
<td>In infants and young children ≤27.5 In adults ≤28.0</td>
<td>A sensitive indicator that falls within days of onset of iron-deficient erythropoiesis and is unaffected by inflammation. It is an excellent tool to recognize ID as well as IDA. False normal values can occur when MCV is increased and in thalassemia. It is not yet widely available on hematology analyzers.</td>
</tr>
<tr>
<td>Serum transferrin receptor (sTfR)</td>
<td>Cutoff varies with assay and with patient’s age and ethnic origin</td>
<td>This soluble receptor is upregulated in ID and is found in increased amounts in serum. It also increased during enhanced erythropoiesis. sTfR is not substantially affected by the acute-phase response, but it might be affected by malaria, age, and ethnicity. Its application is limited by high cost of commercial assays and lack of an international standard, but it has great promise as an indicator of ID.</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>&lt;16%</td>
<td>It is inexpensive, but its use is limited by diurnal variation in serum iron and by many clinical disorders that affect transferrin concentrations including in inflammatory conditions.</td>
</tr>
<tr>
<td>Erythrocyte zinc protoporphyrin (ZPP) (µmol/mol heme)</td>
<td>≤5 yr &gt;70 Children &gt;5 yr &gt;80 Children &gt;5 yr on washed red cells &gt;40</td>
<td>It can be measured directly on a drop of blood with a portable hematofluorometer. A useful screening test in field surveys, particularly in children, in whom uncomplicated ID is the primary cause of anemia. Lead poisoning can increase values, particularly in urban and industrial settings.</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>To be defined; usually ≤10 ng/mL</td>
<td>Extremely elevated in anemia of inflammation and suppressed in iron deficiency anemia.</td>
</tr>
</tbody>
</table>


Table 455-2  Laboratory Studies Differentiating the Most Common Microcytic Anemias

<table>
<thead>
<tr>
<th>STUDY</th>
<th>IRON-DEFICIENCY ANEMIA</th>
<th>α- OR β-THALASSEMA</th>
<th>ANEMIA OF CHRONIC DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>MCV</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal-decreased</td>
</tr>
<tr>
<td>RDW</td>
<td>Increased</td>
<td>Normal or minimally increased</td>
<td>Normal-increased</td>
</tr>
<tr>
<td>RBC</td>
<td>Decreased</td>
<td>Normal-increased</td>
<td>Normal-decreased</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Decreased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Total Fe binding capacity</td>
<td>Increased</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Decreased</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>FEP</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Transferrin receptor</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Reticulocyte hemoglobin concentration</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal-decreased</td>
</tr>
</tbody>
</table>


Volume require the use of age-related standards for recognizing microcytosis (see Table 447-1). The red blood cell count also decreases. The reticulocyte percentage may be normal or moderately elevated, but absolute reticulocyte counts indicate an insufficient response to the degree of anemia. The blood smear reveals hypochromic, microcytic red cells with substantial variation in cell size. Elliptocytic or cigar-shaped red cells are often seen (Fig. 455-1). Detection of increased soluble transferrin receptor and decreased reticulocyte hemoglobin concentration provide very useful and early indicators of iron deficiency, but their availability is more limited.

White blood cell count is normal, and thrombocytosis is often present. Thrombocytopenia is occasionally seen with iron deficiency,
potentially confusing the diagnosis with bone marrow failure disorders. Stool for occult blood should be checked to exclude blood loss as the cause of iron deficiency.

A presumptive diagnosis of iron-deficiency anemia is most often made by a complete blood count demonstrating a microcytic anemia with a high red cell distribution width, reduced red blood cell count, normal white blood cell count, and normal or elevated platelet count. Other laboratory studies, such as reduced serum ferritin, reduced serum iron, and increased total iron-binding capacity, are not usually necessary unless severe anemia requires a more rapid diagnosis, other complicating clinical factors are present, or the anemia does not respond to iron therapy. An increase in hemoglobin ≥1 g/dL after a month of iron therapy is usually the most practical means to establish the diagnosis.

A diagnosis of iron deficiency in the absence of anemia is more challenging. Serum ferritin is a useful measure whose value is increased by also measuring C-reactive protein to help identify false negative results because of concomitant inflammation. Detection of increased soluble transferrin receptor and decreased reticulocyte hemoglobin concentration may find increasing use as they become more available.

Differential Diagnosis
The most common alternative causes of microcytic anemia are α- or β-thalassemia and other hemoglobinopathies, including hemoglobins E and C (see Chapter 462.9). The anemia of inflammation is usually normocytic but can be microcytic in a minority of cases (see Chapter 451.1). Lead poisoning can cause microcytic anemia, but more often the microcytic anemia is due to iron deficiency causing pica and secondary lead intoxication (see Chapter 721). Table 455-2 compares the use of laboratory studies in the diagnosis of the most common microcytic anemias. Other etiologies of microcytic anemia are found in Table 455-3. Although the platelet count can be abnormal, the white blood cell count and neutrophil count should be normal.

When anemia is identified solely by hemoglobin or hematocrit, 60% of children in developed countries have anemia not because of iron deficiency. Caution should be used in treating these children with iron without the benefit of a complete blood and differential count to ensure that a more serious diagnosis is not missed.

Prevention
Iron deficiency is best prevented to avoid both its systemic manifestations and the anemia. Breastfeeding should be encouraged, with the addition of supplemental iron at 4 mo of age. Infants who are not breastfed should only receive iron-fortified formula (12 mg of iron per liter) for the first year, and thereafter cow’s milk should be limited to <20-24 oz daily. This approach encourages the ingestion of foods richer in iron and prevents blood loss as a result of cow’s milk–induced enteropathy.

When these preventive measures fail, routine screening helps prevent the development of severe anemia. Routine screening using hemoglobin or hematocrit is done at 12 mo of age, or earlier if at 4 mo of age the child is assessed to be at high risk for iron deficiency. Therefore screening should continue if risk factors are identified.

Treatment
The regular response of iron-deficiency anemia to adequate amounts of iron is a critical diagnostic and therapeutic feature (Table 455-4). Oral administration of simple ferrous salts (most often ferrous sulfate) provides inexpensive and effective therapy. There is no evidence that the addition of any trace metal, vitamin, or other hematinic substance significantly increases the response to simple ferrous salts. Aside from the unpleasant taste of iron, intolerance to oral iron is uncommon in young children. In contrast, older children and adolescents sometimes have GI complaints.

The therapeutic dose should be calculated in terms of elemental iron. A daily total dose of 3-6 mg/kg of elemental iron in 3 divided doses is adequate, with the higher dose used in more severe cases. The maximum dose would be 150-200 mg of elemental iron daily. Ferrous sulfate is 20% elemental iron by weight and is ideally given between meals with juice, although this timing is usually not critical with a therapeutic dose. Parenteral iron preparations are only used when malabsorption is present or when compliance is poor, because oral therapy is otherwise as fast, as effective, much less expensive and less toxic. When necessary, parenteral iron sucrose, ferric carboxymaltose, and ferric gluconate complex have a lower risk of serious reactions than iron dextran, although only the latter is FDA approved for use in children.

Iron therapy may increase the virulence of malaria and certain Gram-negative bacteria, particularly in developing countries. Iron overdose is associated with *Yersinia* infection.
In addition to iron therapy, dietary counseling is usually necessary. Excessive intake of milk, particularly cow's milk, should be limited. Iron deficiency in adolescent girls secondary to menorrhagia is treated with iron and menstrual control with hormone therapy (see Chapter 116.2).

If the anemia is mild, the only additional study is to repeat the blood count approximately 4 wk after initiating therapy. At this point, the hemoglobin has usually risen by at least 1-2 g/dL and has often normalized. If the anemia is more severe, earlier confirmation of the diagnosis can be made by the appearance of a reticulocytosis usually within 48-96 hr of instituting treatment. The hemoglobin will then begin to increase 0.1-0.4 g/dL per day depending on the severity of the anemia. Iron medication should be continued for 2-3 mo after blood values normalize to reestablish iron stores. Good follow-up is essential to ensure a response to therapy. When the anemia responds poorly or not at all to iron therapy, there are multiple considerations, including diagnoses other than iron deficiency (see Table 455-3).

Because a rapid hematologic response can be confidently predicted in typical iron deficiency, blood transfusion is rarely necessary. It should only be used when heart failure is imminent or if the anemia is severe with evidence of substantial ongoing blood loss. Unless there is active bleeding, transfusions must be given slowly to avoid precipitating or exacerbating congestive heart failure.

*Bibliography is available at Expert Consult.*
Chapter 455  •  Iron-Deficiency Anemia 2326.e1

Bibliography
DEFECTS OF IRON METABOLISM

Rare microcytic anemias may be associated with defects in iron trafficking and regulation. Most are inherited and usually identified in childhood. They include defects of iron absorption, transport, utilization, and recycling. A defect of iron absorption is iron refractory iron deficiency anemia. This defect of transmembrane proteins causes a remarkably severe microcytosis out of proportion to the degree of anemia. This is an autosomal recessive disease due to loss of function mutations in TMPRSS6. In most cases, it is unresponsive to oral iron and partially responsive to intravenous iron. Defects of iron recycling include aceruloplasminemia, in which iron cannot be appropriately transported from macrophages to plasma.

Defects of mitochondrial iron utilization are a diverse group of acquired and inherited defects known as sideroblastic anemias. Impaired heme synthesis leads to retention of iron within the mitochondria of marrow red blood cells (RBCs). The perinuclear distribution of mitochondria results in a pattern of iron staining surrounding the nucleus. These are ringed sideroblasts (Fig. 456-1), which are distinct from the more diffuse cytoplasmic distribution of iron in normal RBC precursors. The anemia is characterized by hypochromic microcytic RBCs mixed with normal RBCs, so the complete blood cell count indicates a very high RBC distribution width. The serum iron concentration usually is elevated, and the transferrin saturation of iron is increased.

Congenital sideroblastic anemia is usually an X-linked disorder and is most commonly a result of mutations in erythrocytic isozyme 5-aminolevulinic acid synthetase, the rate-limiting enzyme reaction in heme synthesis. An important cofactor for 5-aminolevulinic acid synthetase is pyridoxal phosphate. Several of these mutations occur near the binding site for pyridoxal phosphate. Severe anemia is recognized in infancy or early childhood, whereas milder cases might not become apparent until early adulthood or later. Clinical findings include pallor, icterus, and moderate splenomegaly and/or hepatomegaly. The severity of the anemia varies such that some patients require no therapy and others need regular RBC transfusions. A subset of patients with hereditary sideroblastic anemia manifests a hematologic response to pharmacologic doses of pyridoxine. Iron overload as manifested by elevated serum ferritin, elevated serum iron, and increased transferrin saturation is a major complication of this disorder. Clinical evidence of iron overload (e.g., diabetes mellitus, liver dysfunction) may be found in some patients who have little or no anemia. Stem cell transplantation has been used to treat affected children who are dependent on RBC transfusions.

A unique variant of congenital sideroblastic anemia is Pearson syndrome (see Chapter 449), but the anemia is usually macrocytic and not microcytic. Another rare variant of sideroblastic anemia is due to mutations in TRNT1 and manifests with developmental delay, recurrent fevers, and immunodeficiency in addition to anemia.

Acquired sideroblastic anemias can be triggered by drugs and toxins that disturb mitochondrial iron metabolism, including lead and isoniazid. The acquired neoplastic sideroblastic syndromes seen in adults are very rare in children.

Bibliography is available at Expert Consult.
Bibliography


Section 3
Hemolytic Anemias

Chapter 457
Definitions and Classification of Hemolytic Anemias
George B. Segel

Hemolytic Anemias

Hemolysis is defined as the premature destruction of red blood cells (RBCs) (a shortened RBC life span). Anemia results when the rate of destruction exceeds the capacity of the marrow to produce RBCs. Normal RBC survival time is 110–120 days (half-life: 55–60 days), and thus, approximately 0.85% of the most senescent RBCs are removed and replaced each day. During hemolysis, RBC survival is shortened, the RBC count falls, erythropoietin is increased, and the stimulation of marrow activity results in heightened RBC production, reflected in an increased percentage of reticulocytes in the blood. Thus, hemolysis should be suspected as a cause of anemia if an elevated reticulocyte count is present. The reticulocyte count may also be elevated as a response to acute blood loss or for a short period after replacement therapy for iron, vitamin B12, or folate deficiency. The marrow can increase its output 2–3–fold acutely, with a maximum of 6–8–fold in long-standing hemolysis. The reticulocyte percentage can be corrected to measure the magnitude of marrow production in response to hemolysis as follows:

\[
\text{Reticulocyte index} = \frac{\text{reticulocyte\%} \times \frac{\text{Observed hematocrit}}{\text{Normal hematocrit}} \times \frac{1}{\mu}}
\]

where \( \mu \) is a maturation factor of 1–3 related to the severity of the anemia (Fig. 457-1). The normal reticulocyte index is 1.0; therefore, the index measures the fold increase in erythropoiesis (e.g., 2-fold, 3-fold).

As anemia becomes more severe, the erythropoietin concentration increases and reticulocytes are released from the marrow earlier; they are identifiable as reticulocytes in the blood that last for >1 day. Because the reticulocyte index is essentially a measure of RBC production per day, the maturation factor, \( \mu \), provides this correction (see Fig. 457-1).

The erythroid hyperplasia resulting from chronic hemolytic anemia in children, especially thalassemia, may be so extensive that the medullary spaces expand at the expense of the cortical bone. These changes may be evident on physical examination or on radiographs of the skull and long bones (see Fig. 462-7). A propensity to fracture long bones can also occur.

Direct assessment of the severity of hemolysis requires measurement of RBC survival time using RBCs tagged with the radioisotope \( \text{Na}_2^{51}\text{CrO}_4 \). The normal half-life of chromium 51–labeled RBCs is 25–35 days. This value is less than the expected half-life of 55–60 days because of the elution of chromium 51 from the labeled RBCs at the rate of approximately 1% day. Techniques to measure RBC survival using RBC biotin labeling do not require the use of isotopes.

The exaggerated degradation rate of hemoglobin results in increased biliary excretion of heme pigment derivatives and increased urinary and fecal urobilinogen (Fig. 457-2). Gallstones composed of calcium bilirubinate may be formed in children with chronic hemolysis as young as 4 yr of age. Elevations of serum unconjugated bilirubin and lactate dehydrogenase also can accompany hemolysis.

Three heme-binding proteins in the plasma are altered during hemolysis (see Fig. 457-2). Hemoglobin binds to haptoglobin and hemopexin, both of which are cleared more rapidly as conjugates, resulting in a reduced plasma concentration. Oxidized heme binds to albumin to form methemalbumin, which is increased in the plasma. When the capacity of these binding molecules is exceeded, free hemoglobin appears in the plasma, and the pink color can be seen if the plasma is partitioned after centrifugation in a capillary hematocrit tube. If present, free hemoglobin in the plasma is prima facie evidence of intravascular hemolysis. Free hemoglobin dissociates into dimers and is filtered by the kidneys. When the tubular reabsorptive capacity of the kidneys for hemoglobin is exceeded, free hemoglobin appears in the urine. Even in the absence of hemoglobinuria, iron loss can result from reabsorbed hemoglobin and the shedding of renal epithelial cells in which the iron from hemoglobin is stored as hemosiderin. This iron loss can lead to iron deficiency during chronic intravascular hemolysis. When hemoglobin is degraded, an \( \alpha \)-methene bridge is broken in the cyclic tetrapyrrole of the heme moiety, with

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Figure 457-1 Number of days for maturation of reticulocytes to mature erythrocytes in the marrow and blood. The duration of maturation as blood reticulocytes is taken as \( \mu \), which is used in the correction equation in this chapter. (Modified from Hillman RS, Finch CA: Red cell manual, Philadelphia, 1983, FA Davis.)

Figure 457-2 Red cell destruction and catabolism of hemoglobin (Hb) based on the description by Hillman and Finch. Fe, iron. (From Hillman RS, Finch CA: Red cell manual, Philadelphia, 1983, FA Davis.)
release of carbon monoxide (CO) (see Fig. 457-2). The amount of CO in the blood or expired air provides a dynamic measure of the hemolytic rate; end-tidal CO is not available in most clinical laboratories to measure hemolysis.

The hematocrit level depends on the severity of hemolysis and on the erythropoietic response. The shortened RBC life span and heightened RBC production result in a marked susceptibility to aplastic or hypoplastic crises, characterized by erythroid marrow failure and reticulocytopenia, accompanied by a rapid reduction in hemoglobin and hematocrit to extremely low levels. The most common cause of aplastic crisis is infection with parvovirus B19, which is erythrocytropic (see Chapters 251 and 450). An aplastic crisis can produce a precipitous and life-threatening decline in hematocrit that usually lasts 10-14 days. Such transient erythroid marrow failure has only a mild effect in persons with a normal RBC life span, but it has a proportionately greater effect if the RBC life span is shortened by hemolysis. A second infection with parvovirus B19 is uncommon, but other infections can compromise erythroid marrow output, resulting in various degrees of hypoplasia or hypoplastic crises.

Hemolytic anemias may be classified as either cellular, resulting from intrinsic abnormalities of the membrane, enzymes, or hemoglobin; or extracellular, resulting from antibodies, mechanical factors, or plasma factors. Most cellular defects are inherited (paroxysmal nocturnal hemoglobinuria is acquired), and most extracellular defects are acquired (abetalipoproteinemia with acanthocytosis is inherited).

Table 457-1 shows the most common hemolytic anemias, their underlying defects, the diagnostic laboratory tests, and recommendations for treatment.

<table>
<thead>
<tr>
<th>Table 457-1</th>
<th>Hemolytic Anemias and Their Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIAGNOSIS</strong></td>
<td><strong>DEFECT</strong></td>
</tr>
<tr>
<td>Cellular Defects</td>
<td>Membrane Defects</td>
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<tr>
<td>Hereditary spherocytosis</td>
<td>Cytoskeletal protein defects</td>
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<td></td>
<td>Often involve vertical interactions</td>
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<td></td>
<td>of spectrin ankyrin, protein 3</td>
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<td>Abnormal cytoskeletal protein analysis</td>
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<td>Hereditary elliptocytosis</td>
<td>Cytoskeletal protein defects</td>
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<tr>
<td></td>
<td>Often involve horizontal</td>
</tr>
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<td></td>
<td>interactions of spectrin, protein 4.1, and glycophorin c</td>
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<td>Hereditary pyropoikilocytosis</td>
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<tr>
<td></td>
<td>Homozygous or double</td>
</tr>
<tr>
<td></td>
<td>heterozygous abnormality in horizontal interactions of α-spectrin</td>
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<td>Hereditary stomatocytosis</td>
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</tr>
<tr>
<td></td>
<td>Decreased protein 7.2b (1 subset)</td>
</tr>
<tr>
<td></td>
<td>Abnormal RBC cation and water content</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Primary acquired marrow disorder</td>
</tr>
<tr>
<td></td>
<td>RBCs unusually sensitive to complement-mediated lysis</td>
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<tr>
<td>Enzyme Deficiencies</td>
<td>Pyruvate kinase deficiency</td>
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<tr>
<td>G6PD deficiency</td>
<td>A− type: age-labile enzyme</td>
</tr>
<tr>
<td></td>
<td>Mediterranean type: no enzyme activity in circulating RBCs</td>
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</tbody>
</table>

For discussion of hemoglobinopathies, see sections on these topics.
### Table 457-1 Hemolytic Anemias and Their Treatment—cont’d

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>DEFECT</th>
<th>LABORATORY TESTS</th>
<th>TREATMENT</th>
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<tr>
<td><strong>Autoimmune</strong></td>
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</tr>
<tr>
<td>“Warm” antibody</td>
<td>Alteration in membrane surface antigen (Rh)</td>
<td>Spherocytes on blood film</td>
<td>If Hb &gt; 10 g/dL and reticulocyte count &lt; 10%—none</td>
</tr>
<tr>
<td></td>
<td>or abnormal response of B lymphocytes,</td>
<td>Positive direct antiglobulin (Coombs) test to</td>
<td>Severe anemia may require transfusion; prednisone, 2 mg/kg/24 hr</td>
</tr>
<tr>
<td></td>
<td>causing autoantibody formation</td>
<td>IgG “warm” antibody or anti-C3d directed against RBCs</td>
<td>IVIG</td>
</tr>
<tr>
<td></td>
<td>“Molecular mimicry” to viral antigen</td>
<td>Positive indirect Coombs test and antibody detectable in plasma</td>
<td>Rituximab</td>
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<td></td>
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<td>Thermal amplitude 35-40°C (95-104°F)</td>
<td>Splenectomy</td>
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<td>Some complement (C3b) may be detected on RBCs</td>
<td>Immunosuppressives</td>
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<td></td>
<td>Tests for underlying disease</td>
<td>Folic acid, 1 mg/24 hr if chronic</td>
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<td></td>
<td></td>
<td>Spherocytes on blood film</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Positive direct Coombs test to complement (C3b)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Positive indirect Coombs test and antibody detectable in plasma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thermal amplitude 35-40°C (95-104°F)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some complement (C3b) may be detected on RBCs</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Tests for underlying disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serology for infectious mononucleosis; anti-i present</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serology for Mycoplasma pneumoniae; anti-I present</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If Hb &gt; 10 g/dL and reticulocyte count &lt; 10%—none</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe anemia may require transfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid exposure to cold</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If severe:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rituximab</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Immunosuppressives and plasmapheresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisone is less effective</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Splenectomy is not useful</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Folic acid, 1 mg/24 hr if chronic</td>
<td></td>
</tr>
<tr>
<td>“Cold” antibody</td>
<td>“Cold” or IgM autoantibody directed against I/i antigen system</td>
<td>Agglutination or rouleaux on blood film</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive direct Coombs test to complement (C3b)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tests for underlying disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serology for infectious mononucleosis; anti-i present</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Serology for Mycoplasma pneumoniae; anti-I present</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If Hb &gt; 10 g/dL and reticulocyte count &lt; 10%—none</td>
<td></td>
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<td></td>
<td>Severe anemia may require transfusion</td>
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<td></td>
<td></td>
<td>Avoid exposure to cold</td>
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<tr>
<td></td>
<td></td>
<td>If severe:</td>
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<tr>
<td></td>
<td></td>
<td>Rituximab</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppressives and plasmapheresis</td>
<td></td>
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<td></td>
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<td>Prednisone is less effective</td>
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<tr>
<td></td>
<td></td>
<td>Splenectomy is not useful</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Folic acid, 1 mg/24 hr if chronic</td>
<td></td>
</tr>
<tr>
<td>Fragmentation Hemolysis</td>
<td>DIRECT damage to RBC membrane</td>
<td>Fragments on blood film</td>
<td>Treat underlying condition: cytopenias all usually mild</td>
</tr>
<tr>
<td>DIC, TTP, HUS, aHUS, pneumococcal-induced HUS</td>
<td></td>
<td></td>
<td>Splenectomy if complicating other anemia (e.g., thalassemia major)</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>Direct damage to RBC membrane</td>
<td>Fragments on blood film</td>
<td>Folic acid, 1 mg/24 hr</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>Direct damage to RBC membrane</td>
<td>Fragments on blood film</td>
<td></td>
</tr>
<tr>
<td>Burns, thermal injury</td>
<td>Direct damage to RBC membrane</td>
<td>Spherocytes on blood film</td>
<td></td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>Effects of sequestration, ↓ pH, lipases and other enzymes, and macrophages on RBCs</td>
<td>Thrombocytopenia and neutopenia</td>
<td>Folic acid, 1 mg/24 hr</td>
</tr>
<tr>
<td>Plasma Factors</td>
<td>Alteration in plasma cholesterol and phospholipids</td>
<td>Target cells or spiculated RBCs on blood film</td>
<td>Treat underlying condition: cytopenias all usually mild</td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
<td>Abnormal liver function tests</td>
<td>Splenectomy if complicating other anemia (e.g., thalassemia major)</td>
</tr>
<tr>
<td>Abetalipoproteinemia</td>
<td>Absence of apolipoprotein β</td>
<td>Acanthocytes on blood film</td>
<td>Folic acid, 1 mg/24 hr</td>
</tr>
<tr>
<td>Infections</td>
<td>Vitamin E deficiency and heightened sensitivity to oxidative damage</td>
<td>Absent chylomicrons, VLDL, and LDL</td>
<td>Vitamin E (A, K, and D)</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Toxic effects on RBCs</td>
<td>Associated symptoms and signs</td>
<td>Dietary restriction of triglycerides</td>
</tr>
<tr>
<td></td>
<td>membrane, usually self-limited</td>
<td>Cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spherocytes on blood film</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Copper, ceruloplasmin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kaiser Fleischer rings</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penicillamine challenge and urine copper excretion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver biopsy for Cu content</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gene analysis for mutation of ATP7B</td>
<td></td>
</tr>
</tbody>
</table>

aHUS, atypical hemolytic uremic syndrome; Cu, copper; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; HUS, hemolytic uremic syndrome; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; LDL, low-density lipoprotein; K<sub>m</sub>, Michaelis constant; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura; VLDL, very-low-density lipoprotein; V<sub>max</sub>, maximal velocity; WBC, white blood cell.

Hereditary spherocytosis (HS) is a common cause of hemolysis and hemolytic anemia, with a prevalence of approximately 1 in 5,000 persons. It is the most common inherited abnormality of the red blood cell (RBC) membrane. Although common among persons of Northern European origin, HS has been described in most ethnic groups. The more rare defects found in the United States and in Europe are the more common mutations described in the Japanese population. The clinical spectrum varies widely. Affected patients may be asymptomatic, without anemia and with minimal hemolysis, or they may have severe hemolytic anemia requiring regular blood transfusions and a splenectomy.

**ETIOLOGY**

Hereditary spherocytosis usually is transmitted as an autosomal dominant or, less commonly, as an autosomal recessive disorder. As many as 25% of patients have no previous family history. Of these patients, most represent new mutations, and a few cases result from recessive inheritance or represent nonpaternity. The pathophysiology underlying HS involves 5 proteins, which are key components of the cytoskeleton responsible for RBC shape (Table 458-1). Abnormalities of spectrin or ankyrin are the most common molecular defects. Dominant defects have been described in β-spectrin and band 3. Recessive defects have been described in α-spectrin and protein 4.2. Both dominant and recessive defects have been described in ankyrin (Table 458-1). A deficiency in spectrin, band 3, ankyrin, or protein 4.2 results in uncoupling in the “vertical” interactions of the lipid bilayer skeleton and subsequent release of membrane microvesicles. The loss of membrane surface area without a proportional loss of cell volume causes sphering of the RBCs, and an associated increase in cation permeability of the RBC membrane (see Fig. 458-1). Evidence of hemolysis includes reticulocytosis and indirect hyperbilirubinemia. The mean corpuscular hemoglobin level usually is 6–10 g/dL, but it can be in the normal range. The reticulocyte percentage often is increased to 5–10%, with a mean of approximately 10%. The mean corpuscular volume is reduced, and the mean corpuscular hemoglobin concentration is increased.

**CLINICAL MANIFESTATIONS**

In the neonatal period, HS is a significant cause of hemolytic disease and can be manifest as anemia and hyperbilirubinemia sufficiently severe to require phototherapy or exchange transfusions. Hemolysis may be more prominent in the newborn because hemoglobin F binds 2,3-diphosphoglycerate poorly, and the increased level of free 2,3-diphosphoglycerate destabilizes interactions among spectrin, actin, and protein 4.1 in the RBC membrane (see Fig. 458-1). The need for exchange transfusion at birth or transfusions in infancy is not indicative of more severe disease later in life because infants do not mount an adequate reticulocyte response until several months after birth.

Some patients remain asymptomatic into adulthood, but others have severe anemia with pallor, jaundice, fatigue, and exercise intolerance. Severe cases may be marked by expansion of the diploë of the skull as a result of narrow hyperplasia (frontal bossing), but to a lesser extent than in thalassemia major. Depending on the severity of the anemia and the comorbidities associated with severe anemia, some patients benefit from a splenectomy (Table 458-2).

After infancy, splenomegaly is common; there is no correlation between spleen size and disease severity. Bilirubin gallstone formation is a function of age; they can form as early as age 4–5 yr and are present in the majority of adult patients.

Children with HS are also susceptible to aplastic crises, primarily as a result of parvovirus B19 infection, and to hypoplastic crises associated with various other infections (Fig. 458-3). High RBC turnover in the setting of erythroid marrow failure can result in profound anemia (hematocrit <10%), high-output heart failure, cardiovascular collapse, and death. White blood cell and platelet counts can also fall (Fig. 458-3). Rare complications associated with HS include splenic sequestration crisis, gout, cardiomyopathy, priapism, leg ulcers, and spinocerebellar degeneration.

**DIAGNOSIS**

Evidence of hemolysis includes reticulocytosis and indirect hyperbilirubinemia. The hemoglobin level usually is 6–10 g/dL, but it can be in the normal range. The reticulocyte percentage often is increased to 6–20%, with a mean of approximately 10%. The mean corpuscular volume is reduced, and the mean corpuscular hemoglobin concentration is increased. The reticulocyte percentage often is increased to 5–10%, with a mean of approximately 10%. The mean corpuscular volume is reduced, and the mean corpuscular hemoglobin concentration is increased. The reticulocyte percentage often is increased to 5–10%, with a mean of approximately 10%. The mean corpuscular volume is reduced, and the mean corpuscular hemoglobin concentration is increased. The reticulocyte percentage often is increased to 5–10%, with a mean of approximately 10%. The mean corpuscular volume is reduced, and the mean corpuscular hemoglobin concentration is increased.

**Table 458-1: Common Gene Mutations in Hereditary Spherocytosis**

<table>
<thead>
<tr>
<th>PROTEIN</th>
<th>GENE</th>
<th>COMMON MUTATIONS*</th>
<th>PREVALENCE</th>
<th>INHERITANCE</th>
<th>DISEASE SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankyrin-1</td>
<td>ANK1</td>
<td>Frameshift</td>
<td>50-67%</td>
<td>Dominant and recessive</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsense</td>
<td>5-10% in Japan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Splicing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missense</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promoter region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Band 3</td>
<td>AE1 (SLC4A1)</td>
<td>Missense</td>
<td>15-20%</td>
<td>Mostly dominant</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsense</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polymorphism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutant protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Spectrin</td>
<td>SPTB</td>
<td>Null</td>
<td>15-20%</td>
<td>Dominant</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsense</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missense</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polymorphism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Spectrin</td>
<td>SPTA1</td>
<td>Splicing</td>
<td>&lt;5%</td>
<td>Recessive</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>αLEPRA allele</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein 4.2</td>
<td>EPB42</td>
<td>Missense</td>
<td>&lt;5%</td>
<td>Recessive</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsense</td>
<td>45-50% in Japan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Splicing</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Figure 458-1 A simplified cross-section of the red blood cell (erythrocyte) membrane. The lipid bilayer forms the equator of the cross-section with its polar heads (small circles) turned outward. 4.1 R, protein; 4.2, protein 4.2; LW, Landsteiner-Wiener glycoprotein; Rh, Rhesus polypeptide; RhAG, Rh-associated glycoprotein. (From Perrotta S, Gallagher PG, Mohandas N: Hereditary spherocytosis, Lancet 372:1411–1426, 2008.)

Table 458-2 Hereditary Spherocytosis Disease Classification

<table>
<thead>
<tr>
<th>TRAIT</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>Normal</td>
<td>11-15</td>
<td>8-12</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>Normal</td>
<td>&lt;3</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;17</td>
<td>17-34</td>
<td>&gt;34</td>
</tr>
<tr>
<td>Transfusions</td>
<td>0</td>
<td>0</td>
<td>0-2</td>
</tr>
<tr>
<td>Typical heredity</td>
<td>AD</td>
<td>AD</td>
<td>AD or de novo mutation</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>May be indicated*</td>
</tr>
</tbody>
</table>

*Splenectomy indicated if patient requires frequent transfusions for hypoplastic crises or shows poor growth or cardiomegaly.

AD, autodominant; AR, autorecessive.

patients having a family-specific private mutation can be detected by DNA analysis.

**DIFFERENTIAL DIAGNOSIS**

The major alternative considerations when large numbers of spherocytes are seen on the blood smear are isoimmune and autoimmune hemolysis. Isoimmune hemolytic disease of the newborn, particularly when a result of ABO incompatibility, mimics the cell appearance of HS. The detection of antibody on an infant’s RBCs using a direct anti-globulin (Coombs) test should establish the diagnosis of immune hemolysis. Autoimmune hemolytic anemias also are characterized by spherocytes; however, there may be evidence of previously normal values for hemoglobin, hematocrit, and reticulocyte count. Rare causes of spherocytosis include thermal injury, clostridial septicemia, and Wilson disease, each of which can manifest as transient hemolytic anemia (see Table 457-1 in Chapter 457).

**TREATMENT**

**General Supportive Care**

Parents should be advised of the risk of newborn jaundice and the potential need for phototherapy and exchange transfusion after birth to decrease bilirubin levels. Infants born to parents with known HS should be monitored carefully as hyperbilirubinemia may peak several days after birth. A minority of infants will be transfusion-dependent.
until development of adequate erythropoiesis to compensate for the ongoing hemolysis. Continued transfusion-dependence is not common after 6-12 mo of age.

Once the baseline level of disease severity is reached, an annual visit to the hematologist usually is sufficient. Growth should be monitored, exercise tolerance and spleen size documented, and parents should receive anticipatory guidance regarding the risk of aplastic crisis secondary to parvovirus, and hypoplastic crises with other infections. Parents and patients should be informed of an increased risk for gallstone development. The degree of splenomegaly does not correlate with disease severity. Folic acid supplementation is recommended in moderate and severe HS because of an enhanced requirement with increased erythropoiesis.

Guidelines for Splenectomy

Because the spherocytes are destroyed almost exclusively in the spleen, splenectomy eliminates most of the hemolysis. After splenectomy, the anemia, hyperbilirubinemia, and incidence of gallstones are significantly lessened, if not completely eradicated. However, splenectomy is associated with immediate surgical morbidities in addition to a lifelong increased risk for sepsis, particularly that caused by pneumococcal species. This risk is not completely eliminated with the requisite preoperative and postoperative vaccination against pneumococcus, meningococcus, and Haemophilus influenzae type b.

Splenectomy is recommended for patients with severe HS. It should be considered for patients with moderate HS and frequent hypoplastic or aplastic crises, poor growth, or cardiomegaly. It is generally not recommended for patients with mild HS. When splenectomy is indicated, it should be performed after the age of 6 yr, if possible, to avoid the heightened risk of postsplenectomy sepsis in younger children. The laparoscopic approach has less surgical morbidity and is recommended if the surgeon is adequately trained in this approach. Partial splenectomy may be beneficial but needs further study. In children undergoing splenectomy, a concomitant cholecystectomy should be performed if there are gallstones. It is controversial whether to perform a concomitant splenectomy in less-severely ill patients who are undergoing cholecystectomy for gallstone disease. Postsplenectomy thrombocytosis is commonly observed, but requires no treatment and usually resolves spontaneously. Vaccines for encapsulated organisms, such as pneumococcus, meningococcus, and H. influenzae type b, should be administered at least 14 days before splenectomy, and prophylactic oral penicillin VK prescribed indefinitely.

Bibliography is available at Expert Consult.
Bibliography
Hereditary elliptocytosis is a less common disorder than spherocytosis and also varies markedly in severity. Mild hereditary elliptocytosis produces no symptoms; more severe varieties can result in neonatal poikilocytosis (shape variation) and hemolysis, chronic or sporadic hemolytic anemia, or hereditary pyropoikilocytosis (HPP), which is a severe disorder with microspherocytic cells (see Fig. 458-4C). The red blood cells (RBCs) have heightened sensitivity to heat, hence the “pyro” designation. These patients usually inherit a mutant spectrin from one parent, who has mild or no elliptocytosis (silent carrier), and a partial spectrin deficiency from the other parent, who is hematologically normal.

**Ovalocytes**, in contrast to elliptocytes, are less elongated and might reflect a condition known as Southeast Asian ovalocytosis (SAO). SAO is associated with an abnormal protein 3, which functions as an anion exchanger. This disorder can produce neonatal hyperbilirubinemia, but it causes little hemolysis later. It might offer protection against Plasmodium falciparum malaria because normal protein 3 is one of the malarial receptors. Protein 3 as an anion exchanger can cause distal renal tubular acidosis in association with SAO.

**LABORATORY FINDINGS**

The blood film is the most important test to establish hereditary elliptocytosis (see Fig. 458-4B). The RBCs show various degrees of elongation and can actually be rod shaped. In hereditary elliptocytosis, other abnormal RBC shapes may be present, depending on the severity of hemolysis. They include microcytes, spherocytes, and other poikilocytes. The increase in the reticulocyte percentage reflects the severity of hemolysis; erythroid hyperplasia and indirect hyperbilirubinemia may be present. Increased thermal instability is characteristic of HPP. The abnormal spectrin denatures and the cells lyse at 45-46°C (113-114.8°F) instead of the usual 49-50°C (120.2-122°F). The specific protein abnormality can be established by protein separation and analysis techniques. The eosin-5-maleimide binding test, which detects binding to protein band 3 by flow cytometry, may be useful in conjunction with the mean corpuscular volume in diagnosing hereditary elliptocytosis and hereditary spherocytosis. Molecular defects are defined only in research laboratories.

**TREATMENT**

If hereditary elliptocytosis represents a morphologic abnormality on the blood film without evident hemolysis, no treatment is necessary. Patients with chronic hemolysis should receive folic acid. 1 mg daily, to prevent secondary folic acid deficiency. Splenectomy decreases the
hemolysis and should be considered if the hemoglobin is <10 g/dL and the reticulocyte count is >10%. The RBCs on the blood film may be more abnormal after splenectomy, even though hemoglobin increases and reticulocytes decrease. The hematologic features of SAO do not require treatment beyond the newborn period.

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


Hereditary stomatocytosis includes a rare group of dominantly inherited hemolytic anemias in which there are characteristic morphologic changes in the red blood cells (RBCs) and increased red cell cation permeability. The RBCs are cup-shaped, creating a mouth-shaped area (stoma) of central pallor instead of the usual circular area of central pallor. Hereditary stomatocytosis is classified by the RBC hydration status. The 2 major varieties are either overhydrated (hydrocytosis) or dehydrated (xerocytosis).

**HYDROCYTOSIS**

**Pathophysiology**

Stomatocytes of the hydrocytic variant have excess intracellular sodium and water content and decreased intracellular potassium content. The principal defect in this variant is an increase in Na⁺ and K⁺ permeability, caused by mutations in rhesus-associated glycoproteins. However, the amount of Na⁺ influx exceeds the K⁺ efflux, and the cells subsequently develop increased cation content and water, and thus swell. These hydrocytic cells have increased osmotic fragility. Additionally, the integral membrane protein, stomatin or band 7.2 b, is decreased or absent from the erythrocyte membrane. The function of stomatin is not fully understood, although it might act as a switch that influences the function of GLUT1, the glucose transporter. It has been found that stomatin in the hydrocytic variant is synthesized early in RBC development but is lost as the cell matures. The mechanism for this loss of stomatin is not yet determined. It also is unclear how the loss of stomatin expression contributes to the cation leak, which is characteristic of this variant.

**Clinical Features**

The hydrocytic variant is the most severe form of hereditary stomatocytosis and is characterized by moderate to severe hemolysis, macrocytosis, and large numbers of stomatocytes on the blood smear. Patients commonly develop jaundice, splenomegaly, and cholelithiasis.

**XEROCYTOSIS**

**Pathophysiology**

The xerocytic variant is the more common form of hereditary stomatocytosis and usually results in a milder anemia in affected patients. The underlying cation defect is a net loss of RBC potassium that is not accompanied by an increase in sodium. Subsequently, the erythrocyte develops decreased intracellular water content and becomes dehydrated. It may be associated with a syndrome of perinatal edema and ascites. These findings are transient and remain unexplained.

**Clinical Features**

Patients affected by the xerocytic variant have a mild compensated macrocytic hemolytic anemia, variable numbers of stomatocytes and/or target cells on peripheral smear, increased mean corpuscular hemoglobin concentration as a result of the cellular dehydration, and, typically, jaundice and splenomegaly.

**INTERMEDIATE SYNDROMES**

The **Rh deficiency syndrome** is characterized by an absence or profound decrease in the Rh antigen on the RBC membrane. Affected RBCs in this disorder are dehydrated and have decreased cell cation and water content. This decreased cell cation content may be the result of increased potassium leak in spite of increased Na⁺-K⁺ pump activity. This syndrome is associated with mild to moderate hemolytic anemia, reticulocytosis, and stomatocytes and spherocytes on the blood smear.

**Cryohydrocytosis** is a mild form of stomatocytosis, typically caused by mutations in SLC4A1 coding for the band 3 anion exchanger, in which the RBCs lyse on cooling in vitro and may be associated with “pseudohyperkalemia.” Absence of high-density lipoproteins (an α-lipoproteinemia or Tangier disease) can lead to hematologic manifestations such as a moderate hemolytic anemia, stomatocytosis, and thrombocytopenia. Affected patients can also have large orange tonsils, hepatosplenomegaly, lymphadenopathy, cloudy corneas, and peripheral neuropathy.

One of the most flagrant forms of stomatocytosis is seen in **phytosterolemia**, another metabolic disorder, in which the absorption of sterols, both cholesterol and its plant-derived relatives (e.g., sitosterol), is unlimited and unselective. The cells are not leaky to cations; there is macrothrombocytopenia and a degree of short stature. The plasma cholesterol may or may not be abnormal, but mass spectrography always shows a massive increase in plant sterol levels.

**OTHER DISORDERS ASSOCIATED WITH STOMATOCYTOSIS**

Acquired stomatocytosis may be seen with liver disease but also in alcoholism, malignancy, and cardiovascular disease. Stomatocytes can be seen on the blood smears of normal patients as a result of drying artifact.

**TREATMENT**

For severe hemolysis, patients might require RBC transfusion. Splenectomy is not recommended as a treatment for cation-leaky hereditary stomatocytosis. It is not effective and predisposes patients to in situ thrombosis after splenectomy. The thrombosis appears related to abnormal adherence of stomatocytic erythrocytes to the vascular endothelium.

*Bibliography is available at Expert Consult.*
Bibliography


Chapter 461
Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis
George B. Segel

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Etiology
Paroxysmal nocturnal hemoglobinuria (PNH) reflects an abnormality of marrow stem cells that affects each blood cell lineage. The disease is
an acquired somatic mutation that results in a defect in proteins of the cell membrane that renders the red blood cells (RBCs) and other cells susceptible to damage by normal plasma complement proteins (Fig. 461-1). The deficient membrane-associated proteins include decay-accelerating factor (CD55), the membrane inhibitor of reactive lysis (CD59), the C8 binding protein, and other proteins that normally impede complement lysis at various steps, specifically, the alternative pathway, which is constitutively activated. The underlying defect involves the glycolipid anchor that maintains these protective proteins on the cell surface. Various mutations in the PIGA gene that is involved in glycosylphosphatidylinositol anchor protein biosynthesis have been identified in patients with PNH. Glycosylphosphatidylinositol-deficient cells are found at low frequency in normal persons, suggesting that injury to the normal marrow stem cells provides a selective advantage to the progeny of PNH clones in the genesis of this disease.

Clinical Manifestations
PNH is a rare disorder in children. Approximately 60% of pediatric patients have marrow failure, and the remainder have either intermittent or chronic anemia, often with prominent intravascular hemolysis. Nocturnal and morning hemoglobinuria is a classic finding in adults when hemolysis is worse during sleep; chronic hemolysis is more common. In addition to chronic hemolysis, thrombocytopenia and leukopenia are often characteristic. Hemoglobinuria is rarely seen in children compared to adults with PNH. *Thrombosis and thromboembolic phenomena* are serious complications that may be related to altered glycoproteins on the platelet surface and resultant platelet activation and production of procoagulant microparticles. Abdominal venous thrombosis presents as recurrent episodes of abdominal pain, Budd-Chiari syndrome (hepatic veins), or splenomegaly (splenic vein). Furthermore, released free hemoglobin results in depletion of nitric oxide, fostering vasoconstriction, thrombosis, and pain. Back and head pain may also be prominent. Hypoplastic or aplastic pancytopenia can precede or follow the diagnosis of PNH; rarely, PNH may progress to acute myelogenous leukemia. At the time of presentation, more than 90% of patients with PNH have some blood abnormality (including ~35% with anemia alone, ~15% with anemia and thrombocytopenia, ~7% with anemia and neutropenia, and ~30% with pancytopenia), >10% have abdominal pain, and >5% have thrombosis. The mortality in PNH is related primarily to the development of aplastic anemia or thrombotic complications. The predicted survival rate for children before the development of eculizumab (see Treatment below) was 80% at 5 yr, 60% at 10 yr, and 28% at 20 yr.

**Laboratory Findings**
Hemosiderinuria, an elevated reticulocyte percentage, a low serum haptoglobin, and increased lactic dehydrogenase are common and reflect chronic intravascular hemolysis. Initially, the anemia is normocytic, but if iron deficiency develops, it becomes microcytic. Markedly reduced levels of RBC acetylcholinesterase activity and decay-accelerating factor also are found. Flow cytometry is the diagnostic test of choice for PNH. With the use of anti-CD59 for RBCs and anti-CD55 and anti-CD59 for granulocytes, flow cytometry is more sensitive than the classic RBC lysis (ham or sucrose) tests in detecting these reduced glycolipid-bound membrane proteins. Fluorescent-labeled aerolysin testing can heighten the sensitivity of detection by binding selectively to glycosylphosphatidylinositol anchors.

**Treatment**
Glucocorticoids such as prednisone (2 mg/kg/24 hr) have been used to treat acute hemolytic episodes; the dosage should be tapered as soon as the hemolysis abates. Prolonged antiagulation (heparin or low-molecular-weight heparin) therapy may be of benefit when thromboses occur. Because of chronic urinary loss of iron as hemosiderin, iron therapy may be necessary. Androgens (e.g., fluoxymesterone [Halotestin]), antithymocyte globulin, cyclosporine, and growth factors (e.g., erythropoietin and granulocyte colony-stimulating factor) have been used to treat marrow failure. Bone marrow transplantation is successful in treating some cases; nonmyeloablative transplantation can reduce transplant-related mortality and morbidity. Marrow failure and severe thrombosis are the most serious complications in children. Treatment has included hematopoietic stem cell transplantation if a suitable donor exists. Eculizumab has also resulted in sustained survival in the majority of patients. Eculizumab is an approved and effective treatment for PNH in adults. It is a monoclonal antibody against complement component C5, and it interrupts the excessive complement destruction of RBCs and activation of platelets. It decreases the rate of hemolysis, stabilizes hemoglobin levels, reduces the number of transfusions, and reduces the risk of thrombosis. Survival in adults with PNH treated with eculizumab may not be different from sex- and age-matched control patients from the general population. However, the medication does not improve the hematopoietic clonal expansion or prevent marrow failure. Because of the cost and length of treatment required, particularly in children, it may be most useful in preventing thrombosis, anemia, and other symptoms while stem cell transplant is considered. Before beginning eculizumab, it is recommended to immunize patients with the meningococcal vaccine if the patient hasn’t already received this vaccine. A poor response to eculizumab may be due to polymorphisms in the C5 gene that produce resistance to eculizumab blockades.

**ACANTHOCYTOSIS**
Acanthocytosis is characterized by RBCs with irregular circumferential pointed projections (see Fig. 458-4E). This morphologic finding is seen with alterations in the cholesterol:phospholipid ratio in some patients with liver disease or vitamin E deficiency, and in congenital abetalipoproteinemia or hypoprebetalipoproteinemia, associated with fat malabsorption, neuromuscular abnormalities, and retinitis pigmentosa (see Chapters 86.3 and 630). Normoproteinemic neuroacanthocytosis is also associated with 4 genetically diverse conditions (Table 461-1). These include chorea-acanthocytosis and the rare X-linked McLeod syndrome, which has absence of the KX (Kell) antigen, late-onset myopathy, peripheral neuropathy, chorea, splenomegaly, and hemolysis with acanthocytosis. There is usually >3% acanthocytes on peripheral smear and caudate atrophy noted on MRI. Acanthocytes
also are seen in pantothenate kinase-associated neurodegeneration (dystonia, rigidity, chorea, dysarthria, spasticity, retinopathy) and Huntington disease–like 2. The production of acanthocytes in chorea-acanthocytosis appears related to altered Lyn kinase activity with increased tyrosine phosphorylation and altered linkage of band 3 to other RBC membrane proteins.

In contrast, echinocytes or "burr cells" have a more regular distribution of projections or serrations along the surface of the RBCs. They often are seen as artifact, and less often in end-stage renal disease, and in some patients with liver disease.

_Bibliography is available at Expert Consult._

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INHERITANCE</th>
<th>MUTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorea acanthocytosis</td>
<td>Autosomal recessive</td>
<td>VPS13A (CHAC gene)</td>
</tr>
<tr>
<td>McLeod syndrome</td>
<td>X-linked recessive</td>
<td>XK gene</td>
</tr>
<tr>
<td>Huntington disease–like 2</td>
<td>Autosomal dominant</td>
<td>JPH3</td>
</tr>
<tr>
<td>Pantothenate kinase-associated neurodegeneration</td>
<td>Autosomal recessive</td>
<td>PANK2</td>
</tr>
</tbody>
</table>
**Bibliography**


HEMOGLOBIN DISORDERS

Hemoglobin is a tetramer consisting of 2 pairs of globin chains. Abnormalities in these proteins are referred to as hemoglobinopathies.

More than 800 variant hemoglobins have been described. The most common and useful clinical classification of hemoglobinopathies is based on nomenclature associated with alteration of the involved globin chain. Two hemoglobin gene clusters are involved in the production of hemoglobin and are located at the end of the short arms of chromosomes 16 and 11. Their control is complex, including an upstream locus control region on each respective chromosome and an X-linked control site. On chromosome 16, there are 3 genes within the alpha (α) gene cluster, namely zeta (ζ), alpha 1 (α1), and alpha 2 (α2). On chromosome 11, there are 5 genes within the beta (β) gene cluster, namely epsilon (ε), 2 gamma genes (γ), a delta gene (δ), and a beta gene (B).

The order of gene expression within each cluster roughly follows the order of expression during the embryonic period, fetal period, and eventually childhood. After 8 wk of fetal life, the embryonic hemoglobins, Gower-1 (ζεεε), Gower-2 (αεεε), and Portland (ζζεε), are formed. At 9 wk of fetal life, the major hemoglobin (Hb) is HbF (ααγγ). HbA (ααββ) first appears at approximately 1 mo of fetal life, but does not become the dominant hemoglobin until after birth, when HbF levels start to decline. HbA1c (ααδδ) is a minor hemoglobin that appears shortly before birth and remains at a low level after birth. The final hemoglobin distribution pattern that occurs in childhood is not achieved until at least 6 mo of age and sometimes later. The normal hemoglobin pattern is ≥95% HbA1c, ≤3.5 HbA2c, and <2.5% HbF.

462.1 Sickle Cell Disease

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

Great strides have been made in the management of both acute and chronic complications of sickle cell disease with a significant improvement in the life expectancy of a child born today in the United States. However, the majority of children with sickle cell disease are born outside of the United States with limited access to preventive care and disease-modifying treatments.

Children with sickle cell disease should be followed by experts in the management of this disease, most often by pediatric hematologists. Medical care provided by a pediatric hematologist is also associated with a decreased frequency of emergency department visits and length of hospitalization when compared to patients who were not seen by a hematologist within the last year.

PATHOPHYSIOLOGY

Hemoglobin S (HbS) is the result of a single base-pair change, thymine for adenine, at the sixth codon of the β-globin gene. This change encodes valine instead of glutamine in the 6th position in the β-globin molecule. Sickle cell anemia (HbSS), homozygous HbSS, occurs when both β-globin alleles have the sickle cell mutation (βs). Sickle cell disease refers to not only patients with sickle cell anemia, but also to compound heterozygotes where one β-globin allele includes the sickle cell mutation and the second β-globin allele includes a gene mutation other than the sickle cell mutation, such as HbC, β-thalassemia, HbD, and HbOArab. In sickle cell anemia, HbS is commonly as high as 90% of the total hemoglobin; whereas in sickle cell disease, HbS is >50% of all hemoglobin.

In red blood cells, the hemoglobin molecule has a highly-specified conformation allowing for the transport of oxygen in the body. In the absence of globin-chain mutations, hemoglobin molecules do not interact with one another. However, the presence of HbS results in a conformational change in the hemoglobin tetramer and, in the deoxygenated state, HbS molecules can now interact with each other forming rigid polymers that give the red blood cell its characteristic “sickled” shape. The lung is the only organ capable of reversing the polymers, and any disease of the lung can be expected to compromise the degree of reversibility.

Intravascular sickling primarily occurs in the postcapillary venules and is a function of both mechanical obstruction by sickled red blood cells and increased adhesion between red blood cells, leukocytes and the vascular endothelium. Sickle cell disease is also an inflammatory disease based on nonspecific markers of inflammation, including, but not limited to, elevated baseline white blood cell count and cytokines.

DIAGNOSIS AND EPIDEMIOLOGY

Every state in the United States has instituted a mandatory newborn screening program for sickle cell disease. Such programs identify newborns with the disease and provide prompt diagnosis and referral to providers with expertise in sickle cell disease for anticipatory guidance and the initiation of penicillin before 4 mo of age.

The most commonly used procedures for newborn diagnosis include thin layer/isoelectric focusing and high-performance liquid chromatography (HPLC). A confirmatory step is recommended, with all patients who have initial abnormal screens being retested during the first clinical visit and after 6 mo of age to determine the final hemoglobin phenotype. In addition, a complete blood cell count (CBC) and hemoglobin phenotype determination is recommended for both parents to confirm the diagnosis and to provide an opportunity for genetic counseling. Table 462-1 correlates the initial hemoglobin phenotype at birth with the type of hemoglobinopathy; baseline hemoglobin range, and requirement for a hematologist.

In newborn screening programs, the hemoglobin with the greatest quantity is reported first, followed by other hemoglobins in order of decreasing quantity. In newborns with a hemoglobin analysis result
of FS, the pattern supports HbSS, HbS hereditary persistent fetal hemoglobin (HPFH), or HbS-thalassemia zero. In a newborn with a hemoglobin analysis of FSA, the pattern is supportive of diagnosis HbS-thalassemia+. The diagnosis of HbS-thalassemia+ is confirmed if at least 50% of the hemoglobin is HbS, HbA is present, and the amount of HbA2 is elevated (typically >3.5%); although, HbA2 is not elevated in the newborn period. In newborns with a hemoglobin analysis of FSC, the pattern supports a diagnosis of HbSC. In newborns with a hemoglobin analysis of FAS, the pattern supports a diagnosis of HbAS (sickle cell trait).

A newborn with a hemoglobin analysis of AFS has been transfused with red blood cells prior to collection of the newborn screen because the amount of HbA is greater than the amount of HbF or there has been an error. The patient may have either sickle cell disease or sickle cell trait and should be started on penicillin prophylaxis until the final diagnosis can be determined.

Given the implications of a diagnosis of sickle cell disease versus sickle cell trait in a newborn, repeating the hemoglobin analysis in the patient and obtaining a hemoglobin analysis and CBC to evaluate the smear and red blood cell parameters in the parents for genetic counseling cannot be overemphasized. Unintended mistakes do occur in state newborn screening programs. Newborns who have the initial phenotype of HbFSS but whose final true phenotype included HbS-thalassemia+ have been described as one of the more common errors identified in newborn screening hemoglobinopathy programs. Determining an accurate phenotype is important for appropriate genetic counseling for the parents.

In the event that the parents are tested for sickle cell trait or hemoglobinopathy trait testing, full disclosure must be provided that in some circumstances, the issue of paternity may be disclosed. For this reason and because of healthcare privacy, we always seek permission for the genetic testing and to ensure confidentiality, we report the hemoglobinopathy trait results back separately to each parent during separate visits.

In the United States, sickle cell disease is the most common genetic disorder identified through the state-mandated newborn screening program, occurring in 1:2,467. In regard to race in the United States, sickle cell disease occurs in African-Americans at a rate of 1:396 births, and in Hispanics at a rate of 1:36,000 births. In the United States, an estimated 90,000 people are affected by sickle cell disease, with an ethnic distribution of 90% African-American and 10% Hispanic. The United States sickle cell disease population represents a fraction of the worldwide burden of the disease, with global estimates of 312,000 neonates born annually with HbSS disease.

**Table 462.1 Various Newborn Sickle Cell Disease Screening Results with Baseline Hemoglobin**

<table>
<thead>
<tr>
<th>NEWBORN SCREENING RESULTS: SICKLE CELL DISEASE*</th>
<th>POSSIBLE HEMOGLOBIN PHENOTYPE†</th>
<th>BASELINE HEMOGLOBIN RANGE</th>
<th>EXPERTISE IN HEMATOLOGY CARE REQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS</td>
<td>SCD-SS</td>
<td>6-11 g/dL</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SCD-Sβthal</td>
<td>6-10 g/dL</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SCD-Sβthal</td>
<td>9-12 g/dL</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SCD-Sδβthal</td>
<td>10-12 g/dL</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>S HPFH</td>
<td>12-14 g/dL</td>
<td>Yes</td>
</tr>
<tr>
<td>FSC</td>
<td>SCD-SC</td>
<td>10-15 g/dL</td>
<td>Yes</td>
</tr>
<tr>
<td>FSA</td>
<td>SCD-Sβthal</td>
<td>9-12 g/dL</td>
<td>Yes</td>
</tr>
<tr>
<td>FS other</td>
<td>SCD-Sβthal</td>
<td>6-10 g/dL</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>SCD-SD, SδOArab, SαHbH, SδOArab</td>
<td>Variable</td>
<td>Yes</td>
</tr>
<tr>
<td>AFS</td>
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</tr>
<tr>
<td></td>
<td>SCD-Sβthal</td>
<td>6-9 g/dL</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SCD-Sβthal†</td>
<td>7-13 g/dL variable</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Hemoglobins are reported in order of quantity.
†Requires confirmatory hemoglobin analysis after at least 6 mo of age and, if possible, hemoglobin analysis from both parents for accurate diagnosis of hemoglobin phenotype.
‡Impossible to determine the diagnosis because the infant received a blood transfusion before testing.
A, normal hemoglobin; C, hemoglobin C; F, fetal hemoglobin; HPFH, hereditary persistence of fetal hemoglobin; OArab, hemoglobin OArab; S, sickle hemoglobin; SC, sickle-hemoglobin C; SCD, sickle cell disease; SS, homozygous sickle cell disease; thal, thalassemia.

**CLINICAL MANIFESTATIONS AND TREATMENT OF SICKLE CELL ANEMIA (HB SS)**

**Fever and Bacteremia**

Fever in a child with sickle cell anemia is a medical emergency, requiring prompt medical evaluation and delivery of antibiotics because of the increased risk of bacterial infection and subsequent high mortality rate. Infants with sickle cell anemia, as early as 6 mo of age, develop abnormal immune function due to splenic infarction. By 5 yr of age, most children with sickle cell anemia have complete functional asplenia. Regardless of age, all patients with sickle cell anemia are at increased risk of infection and death from bacterial infection, particularly encapsulated organisms such as Streptococcus pneumoniae, Haemophilus influenzae type b, and Neisseria meningitidis.

The rate of bacteremia in children with sickle cell disease, presenting with fever in busy pediatric emergency department is less than 1%. Several clinical strategies have been developed to manage children with sickle cell anemia who present with fever. These vary from hospital admission for intravenous (IV) antimicrobial therapy to administering a 3rd-generation cephalosporin in an emergency department or outpatient setting to patients without established risk factors for occult bacteremia (Table 462.2). Given the observation that the average time for a positive blood culture is <20 hr in children with sickle cell anemia, admission for 24 hr is probably the most prudent strategy for children and families who live out of town or who are identified as high risk for poor follow-up.

Outpatient management of fever without a source should be considered in children with the lowest risk of bacteremia and after intravenous ceftriaxone or other cephalosporin is given. Observation after antibiotic administration is important as children who have sickle cell anemia who present with fever. These vary from hospital admission for intravenous (IV) antimicrobial therapy to administering a 3rd-generation cephalosporin in an emergency department or outpatient setting to patients without established risk factors for occult bacteremia (Table 462.2). Given the observation that the average time for a positive blood culture is <20 hr in children with sickle cell anemia, admission for 24 hr is probably the most prudent strategy for children and families who live out of town or who are identified as high risk for poor follow-up.

Outpatient management of fever without a source should be considered in children with the lowest risk of bacteremia and after intravenous ceftriaxone or other cephalosporin is given. Observation after antibiotic administration is important as children who have sickle cell anemia treated with ceftriaxone can develop severe, rapid, and life-threatening immune hemolysis. In the event that Salmonella spp. or Staphylococcus aureus bacteremia occurs, strong consideration should be given to an evaluation for osteomyelitis with a bone scan given the increased risk of osteomyelitis in children with sickle cell anemia when compared to the general population.

**Aplastic Crisis**

Human parvovirus B19 poses a unique threat for patients with sickle cell anemia because such infections result in temporary red cell aplasia, limiting the production of reticulocytes and causing profound anemia. Any child with sickle cell disease, fever, and reticulocytopenia should be considered to have parvovirus B19 until proven otherwise. The acute anemia of an aplastic crisis is treated conservatively using...
red blood cell transfusion when the patient becomes hemodynamically symptomatic or has a concurrent illness, such as acute chest syndrome. In addition, acute infection with parvovirus B19 is associated with pain, splenic sequestration, acute chest syndrome (ACS), glomerulonephritis, and stroke. Patients with parvovirus-associated aplastic crisis are contagious and infection precautions should be taken to avoid nosocomial spread of the infection.

**Splenic Sequestration**

Acute splenic sequestration is a life-threatening complication occurring primarily in infants and young children with sickle cell anemia. The incidence of splenic sequestration has declined from an estimated 30% to 12.6% with early identification by newborn screening and parental education. Sequestration can occur as early as 5 wk of age, but most often occurs in children between the ages of 6 mo and 2 yr.

Splenic sequestration is associated with rapid spleen enlargement causing left-sided abdominal pain and a decline in hemoglobin of at least 2 g/dL from the patient’s baseline. Sequestration may lead to signs of hypovolemia as a result of the trapping of blood in the spleen; profound anemia, with total hemoglobin falling below 3 g/dL, has been reported. Reticulocytosis and a decrease in the platelet count may also be present. Sequestration may be triggered by fever, bacteremia, or viral infections.

Treatment includes early intervention and maintenance of hemodynamic stability using isotonic fluid or blood transfusions. Careful blood transfusions with red blood cells are recommended to treat both the sequestration and the resultant anemia. Blood transfusion aborts the red blood cell sickling in the spleen and allows release of the patient’s blood cells that have become sequestered, often raising the hemoglobin above baseline values. We typically recommend only 5 mL/kg of red blood cells because the goal is to prevent hypovolemia.

Blood transfusion that results in hemoglobin levels above 10 g/dL may put the patient at risk for autotransfusion (the phenomenon when the blood sequestered in the spleen is released and dramatically increases the hemoglobin concentration, putting the patient at risk for hyperviscosity syndrome).

**Hepatic and Gallbladder Involvement**

See Chapters 360 and 366.

**Sickle Cell Pain**

Dactylitis, referred to as hand-foot syndrome, is often the first manifestation of pain in infants and young children with sickle cell anemia, occurring in 50% of children by their 2nd yr of life (Fig. 462-1). Dactylitis often manifests with symmetric or unilateral swelling of the hands and/or feet. Unilateral dactylitis can be confused with osteomyelitis, and careful evaluation to distinguish between the two is important because treatment differs significantly. Dactylitis requires palliation with pain medications, such as hydrocodone, whereas osteomyelitis requires at least 4-6 wk of IV antibiotics. Given the recent association between genotype and metabolism of codeine, a subgroup of children may not get pain relief from codeine. Hence, feedback from the parents is needed to determine if therapy was successful in relieving pain.

The cardinal clinical feature of sickle cell anemia is acute vasocclusive pain. No written definition can describe the visual picture of a child with sickle cell anemia experiencing pain. Acute sickle cell pain is characterized as unremitting discomfort that can occur in any part of the body but most often occurs in the chest, abdomen, or extremities. These painful episodes are often abrupt and cause disruption of daily life activities and anguish for children and their caregivers. A patient with sickle cell anemia has approximately 1 painful episode per year that requires medical attention.

The exact etiology of pain is unknown, but the pathogenesis is initiated when blood flow is disrupted in the microvasculature by sickled cells, resulting in tissue ischemia. Acute sickle cell pain may be precipitated by physical stress, infection, dehydration, hypoxia, local or systemic acidosis, exposure to cold, and swimming for prolonged periods. Successful treatment of painful episodes requires education of both the caregivers and patients regarding the recognition of symptoms and the optimal management strategy. Given the absence of any

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**Table 462-2**

<table>
<thead>
<tr>
<th>Clinical Factors Associated with Increased Risk of Bacteremia Requiring Admission in Febrile Children with Sickle Cell Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seriously ill appearance</td>
</tr>
<tr>
<td>Hypotension: systolic blood pressure &lt;70 mm Hg at 1 yr of age or &lt;70 mm Hg + 2 x age in yr for older children</td>
</tr>
<tr>
<td>Poor perfusion: capillary-refill time &gt;4 sec</td>
</tr>
<tr>
<td>Temperature &gt;40.0°C (104°F)</td>
</tr>
<tr>
<td>A corrected white-cell count &gt;30,000/mm³ or &lt;5000/mm³</td>
</tr>
<tr>
<td>Platelet count &lt;100,000/mm³</td>
</tr>
<tr>
<td>History of pneumococcal sepsis</td>
</tr>
<tr>
<td>Severe pain</td>
</tr>
<tr>
<td>Dehydration: poor skin turgor, dry mucous membranes, history of poor fluid intake, or decreased output of urine</td>
</tr>
<tr>
<td>Infiltration of a segment or a larger portion of the lung</td>
</tr>
<tr>
<td>Hemoglobin level &lt;5.0 g/dL</td>
</tr>
</tbody>
</table>

reliable objective laboratory or clinical parameter associated with pain, trust between the patient and the treating physician is paramount to successful clinical management. Specific therapy for pain varies greatly but generally includes the use of acetaminophen or a nonsteroidal antiinflammatory agent early in the course of pain, followed by escalation to a combination analgesic such as hydrocodone, or to a single-agent short- or long-acting oral opioid.

Some patients require hospitalization for administration of intravenous morphine or derivatives of morphine. The incremental increase and decrease in the use of the medication to relieve pain roughly parallels the 8 phases associated with a chronology of pain and comfort (Table 462-3). The average hospital length of stay for children admitted in pain is 4.4 days. The American Pain Society has published clinical guidelines for treating acute and chronic pain in patients with sickle cell disease of any type. These recommendations are comprehensive and represent a starting point for treating pain (http://www.ampainsoc.org/pub/sc.htm).

The only measure for degree of pain is the patient. Healthcare providers working with children in pain should use a consistent, validated pain scale, such as the Wong-Baker FACES Scale for assessing pain. Although pain scales have proved useful for some children, others require prenegotiated activities to determine when opioid therapy should be initiated and decreased. For instance, sleeping through the night might be an indication for decreasing pain medication by 20% the following morning. The majority of painful episodes in patients with sickle cell anemia are managed at home with comfort measures, such as heating blanket, relaxation techniques, massage, and oral pain medication.

Several myths have been propagated regarding the treatment of pain in sickle cell anemia. The concept that painful episodes in children should be managed without opioids is without foundation and results in unwarranted suffering on the part of the patient. Blood transfusion therapy during an existing painful episode does not decrease the intensity or duration of the painful episode as tissue necrosis occurs well before the ability to administer the transfusion. Intravenous hydration does not relieve or prevent pain and is appropriate when the patient is dehydrated or unable to drink as a result of the severe pain. Opioid dependency in children with sickle cell anemia is rare and should never be used as a reason to withhold pain medication. However, patients with multiple painful episodes requiring hospitalization within a year or with pain episodes that require hospitalization for more than 7 days should be evaluated for comorbidities and environmental stressors that are contributing to the frequency or duration of pain. Children with chronic pain should be evaluated for other reasons associated with vasoocclusive pain episodes, including, but not limited to, overexertion with physical activities, such as participating in the school band, sports, or heavy lifting of backpacks to and from school and up and down steps. A careful history is warranted to distinguish chronic pain that often is not relieved by opioids alone versus acute unrelenting vasoocclusive pain episodes.

Skeletal pain (bone or bone marrow infarction) with or without fever must be differentiated from osteomyelitis. Both Salmonella spp. and S. aureus cause osteomyelitis in children with sickle cell anemia, which is often in the diaphysis of long bones (in contrast to children without sickle cell anemia where osteomyelitis is in the metaphyseal region of the bone). Differentiating osteonecrosis from a vasoocclusive

### Table 462-3 Summary of the Chronology of Pain in Children with Sickle Cell Disease

<table>
<thead>
<tr>
<th>PHASE</th>
<th>PAIN CHARACTERISTICS</th>
<th>SUGGESTED COMFORT MEASURES USED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Baseline)</td>
<td>No vasoocclusive pain; pain of complications may be present, such as that connected with avascular necrosis of the hip</td>
<td>No comfort measures used</td>
</tr>
<tr>
<td>2 (Prepain)</td>
<td>No vasoocclusive pain; pain of complications may be present; prodromal signs of impending vasoocclusive episode may appear, e.g., “yellow eyes” and/or fatigue</td>
<td>No comfort measures used; caregivers may encourage child to increase fluids to prevent pain event from occurring</td>
</tr>
<tr>
<td>3 (Pain start point)</td>
<td>First signs of vasoocclusive pain appear, usually in mild form</td>
<td>Mild oral analgesic often given; fluids increased; child usually maintains normal activities</td>
</tr>
<tr>
<td>4 (Pain acceleration)</td>
<td>Intensive of pain increases from mild to moderate</td>
<td>Stronger oral analgesic are given; rubbing, heat, or other activities are often used; child usually stays in school until the pain becomes more severe, then stays home and limits activities; is usually in bed; family searches for ways to control the pain</td>
</tr>
<tr>
<td>5 (Peak pain experience)</td>
<td>Pain accelerates to high moderate or severe levels and plateaus; pain can remain elevated for extended period Child’s appearance, behavior, and mood are significantly different from normal</td>
<td>Oral analgesics are given around the clock at home; combination of comfort measures is used; family might avoid going to the hospital; if pain is very distressing to the child, parent takes the child to the emergency department After child enters the hospital, families often turn over comforting activities to healthcare providers and wait to see if the analgesics work Family caregivers are often exhausted from caring for the child for several days with little or no rest</td>
</tr>
<tr>
<td>6 (Pain decrease start point)</td>
<td>Pain finally begins to decrease in intensity from the peak pain level</td>
<td>Family caregivers again become active in comforting the child but not as intensely as during phases 4 and 5</td>
</tr>
<tr>
<td>7 (Steady pain decline)</td>
<td>Pain decreases more rapidly, become more tolerable for the child Child and family are more relaxed</td>
<td>Healthcare providers begin to wean the child from the IV analgesic; oral opioids given; discharge planning is started Children may be discharged before they are pain free</td>
</tr>
<tr>
<td>8 (Pain resolution)</td>
<td>Pain intensity is at a tolerable level, and discharge is imminent Child looks and acts like “normal” self; mood improves</td>
<td>May receive oral analgesics</td>
</tr>
</tbody>
</table>
Avascular Necrosis

Avascular necrosis (AVN) occurs at a higher rate among children with sickle cell anemia than in the general population, and is a source of both acute and chronic pain. Most commonly, the femoral head is affected and AVN. Unfortunately, the AVN of the hip may cause limp and leg-length discrepancy. Other sites affected include the humeral head and mandible. Risk factors for AVN include HbSS disease with α-thalassemia trait, frequent vasoocclusive episodes, and elevated hematocrit (for patients with sickle cell anemia). Optimal treatment of AVN has not been determined and individual management requires consultation with the disease-specific specialist, orthopedic surgeon, physical therapist, hematologist and primary care physician. Initial management may include referral to a physical therapist to address strategies to increase strength and decrease weight bearing daily activities, periestoial elevation, and bone, periosteal, or extraosseous fluid collections. MRI findings suggestive of osteomyelitis include localized medullary fluid, sequestrum, and cortical defects. Ultimately, aspiration with or without biopsy and culture will be needed to differentiate the 2 processes (see Chapter 684).

Neurologic Complications

Neurologic complications associated with sickle cell anemia are varied and complex, ranging from acute ischemic stroke with focal neurologic deficit to clinically silent abnormalities found on radiologic imaging. Prior to the development of transcranial Doppler to screen for stroke risk among children with sickle cell anemia, approximately 11% experienced an overt stroke and 20% a silent stroke before their 18th birthday. A functional definition of overt stroke is the presence of a focal neurologic deficit lasting for >24 hr and/or abnormal neuroimaging of the brain indicating a cerebral infarct on T2-weighted magnetic resonance imaging (MRI) corresponding to the focal neurologic deficit (Figs. 462-2 and 462-3). A silent cerebral infarct, as its name indicates, lacks focal neurologic findings lasting >24 hr and is diagnosed by abnormal imaging on T2-weighted MRI.

Priapism

Priapism is defined as an unwanted painful erection of the penis and most commonly affects males with sickle cell anemia. The mean age of first episode is 15 yr, although priapism has been reported in children as young as 3 yr. The actuarial probability of a patient experiencing priapism is approximately 90% by 20 yr of age.

Priapism occurs in 2 patterns: prolonged, lasting more than 4 hr, or stuttering, with brief episodes that resolve spontaneously but may occur in clusters and herald a prolonged event. Both types occur from early childhood to adulthood. Most episodes occur between 3 a.m. and 9 a.m. Priapism in sickle cell disease represents a low flow state caused by venous stasis from sickling of red blood cells in the corpora cavernosa. Recurrent prolonged episodes of priapism are associated with impotence.

The optimal treatment for acute priapism is unknown. Acutely, supportive therapy, such as a hot shower, short aerobic exercise, or pain medication, is commonly used by patients at home. A prolonged episode lasting >4 hr should be treated by aspiration of blood from the corpora cavernosa followed by irrigation with dilute epinephrine to produce immediate and sustained detumescence. Urology consultation is required to initiate this procedure, with appropriate input from a hematologist. Simple blood transfusion and exchange transfusion has been proposed for the acute treatment of priapism, but limited evidence supports this strategy as the initial management. We typically refer a patient to the urology service first, and if no benefit is obtained from surgical management, consider transfusion therapy. However, detumescence may not occur for up to 24 hr (far longer than with urologic aspiration) after transfusion and transfusion for priapism has been associated with acute neurologic events.
types of sickle cell disease, such as HbSC or HbSβ-thalassemia+, develop overt or silent cerebral infarcts as well, but at a lower frequency than children with HbSS and HbSβ-thalassemia zero. Other neurologic complications include headaches that may or may not correlate to degree of anemia, seizures, cerebral venous thrombosis and reversible posterior leukoencephalopathy syndrome, also referred to as posterior reversible encephalopathy syndrome (PRES).

For patients presenting with acute focal neurologic deficit, a prompt pediatric neurologic evaluation is recommended, as well as consultation with a pediatric hematologist. In addition, oxygen administration to keep oxygen saturations >96% and simple blood transfusion within 1 hr of presentation with a goal of increasing the hemoglobin to a maximum of 10 g/dL is warranted. A timely simple blood transfusion is important because this is the most efficient strategy to dramatically increase oxygen content of the blood, if the oxygen saturation is above 96%. To exceed this hemoglobin threshold limits oxygen delivery to the brain as a result of hyperviscosity by increasing the hemoglobin significantly over the patient’s baseline values. Subsequently, prompt treatment with an exchange transfusion should be considered, either manually or with automated erythrocytapheresis, to reduce the HbS percentage to at least <50%, and ideally to <30%. Exchange transfusion at the time of acute stroke is associated with a decreased risk of second stroke when compared to simple transfusion alone. Computed tomography (CT) of the head to exclude cerebral hemorrhage should be performed as soon as possible, and if available, MRI of the brain with diffusion-weighted imaging to distinguish between ischemic infarcts and PRES. Magnetic resonance (MR) venography is useful to evaluate the possibility of cerebral venous thrombosis, a rare but potential cause of focal neurologic deficit in children with sickle cell disease. MR angiography may identify evidence of cerebral vasculopathy; these images are not critical in the initial time management of a child with sickle cell disease presenting with a focal neurologic deficit.

The clinical presentation of PRES or central venous thrombosis can mimic a stroke but would require a different treatment course. For both PRES and cerebral venous thrombosis, the optimal management has not been defined in patients with sickle cell disease, resulting in the need for consultation with both a pediatric neurologist and a pediatric hematologist.

**Transcranial Doppler Ultrasonography**

Primary prevention of overt stroke can be accomplished using **transcranial Doppler ultrasonography** (TCD) assessment of the blood velocity in the terminal portion of the internal carotid and the proximal portion of the middle cerebral artery. Children with sickle cell anemia with an elevated time-averaged mean maximum (TAMM) blood-flow velocity >200 cm/sec are at increased risk for a cerebrovascular event. A TAMM measurement of <200 cm/sec but ≥180 cm/sec represents a conditional threshold. A repeat measurement is suggested within a few months because of the high rate of conversion to a TCD velocity >200 cm/sec in this group of patients.

Two distinct methods of measuring TCD velocity exist: a nonimaging and an imaging technique. The nonimaging technique was the method used in the TCD trial sponsored by the National Institutes of Health, whereas most pediatric radiologists in practice use the imaging technique. When compared to each other, the imaging technique produces values that are 10-15% below that of the nonimaging technique. The imaging technique uses the time-averaged mean of the maximum velocity (TAMX), and this measure is believed to be equivalent to the nonimaging calculation of TAMM. A downward adjustment for the transfusion threshold is appropriate for centers using the imaging method to assess TCD velocity. The magnitude of the transfusion threshold in the imaging technique has not been settled, but a transfusion threshold of a TAMX of 185 cm/sec and a conditional threshold of TAMX of 165 cm/sec, seems reasonable.

The primary approach for prevention of recurrent overt stroke is blood transfusion therapy aimed at keeping the maximum HbS concentration <30%. Despite regular blood transfusion therapy, around 20% of patients will have a second stroke and 30% of this group will have a third stroke. Children with TCD values above defined thresholds should begin chronic blood transfusion therapy to maintain HbS levels <30% to decrease the risk of first stroke. This strategy results in an 85% reduction in the rate of overt strokes. Once transfusion therapy is initiated, patients are expected to continue it indefinitely as discontinuation of blood transfusion therapy is associated with an increase in the development of silent infarcts.

**Pulmonary Complications**

**Lung disease** in children with sickle cell anemia is the second most common reason for hospital admission and is associated with significant mortality. ACS refers to a life-threatening pulmonary complication of sickle cell disease defined as a new radiodensity on chest radiography plus any of the following: fever, respiratory distress, hypoxia, cough, or chest pain (Fig. 462-4). Even in the absence of respiratory symptoms, all patients with fever should receive a chest radiograph to identify evolving ACS because clinical examination alone is insufficient to identify patients with a new radiographic density and early detection of ACS will alter clinical management. The radiographic findings in ACS are variable but may include single lobe involvement, predominantly left lower lobe; multiple lobes, most often both lower lobes; and pleural effusions, either unilateral or bilateral. ACS may progress rapidly from a simple infiltrate to extensive infiltrates and a pleural effusion. Therefore, continued pulse oximetry and frequent clinical exams are required, and repeat chest x-rays are indicated for progressive hypoxia, dyspnea, tachypnea, and other signs of respiratory distress.

The majority of patients with ACS do not have a single identifiable cause. Infection is the most well-known etiology, yet only 30% of ACS episodes will have positive sputum or bronchoalveolar culture, and the most common pathogens are *S. pneumoniae*, Mycoplasma pneumoniae, and *Chlamydia* sp. The most frequent event preceding ACS is a painful episode requiring systemic opioid treatment. Fat emboli has also been implicated as a cause of ACS, arising from infarcted bone marrow, and can be life-threatening if large amounts are released to the lungs. Fat
Pulmonary hypertension has been identified as a major risk factor for death in adults with sickle cell anemia. The natural history of pulmonary hypertension in children with sickle cell anemia is unknown. Optimal strategies for screening at risk patients have not been identified (echocardiogram results are not supported by right heart catheterization results demonstrating elevated pulmonary artery pressures) and the best diagnostic methodology carries significant risk of harm. Attempts to identify targeted therapeutic interventions to alter the natural history of pulmonary hypertension in adults have been unsuccessful.

**Renal Disease and Enuresis**

*Renal disease* among patients with sickle cell disease is a major comorbid condition that can lead to premature death. Seven sickle cell disease nephropathies have been identified: (1) gross hematuria, (2) papillary necrosis, (3) nephrotic syndrome, (4) renal infarction, (5) hyperthrombocytopenia, (6) pyelonephritis, and (7) renal medullary carcinoma. As expected, the presentation of these entities is varied but may include

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**Table 462-4** Overall Strategies for the Management of Acute Chest Syndrome

<table>
<thead>
<tr>
<th>PREVENTION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incentive spirometry and periodic ambulation in patients admitted for sickle cell pain, surgery, or febrile episodes</td>
<td>Blood transfusion (simple or exchange)</td>
</tr>
<tr>
<td>Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)</td>
<td>Supplemental O₂ for drop in pulse oximetry by 4% over baseline, or values &lt;90%</td>
</tr>
<tr>
<td>Cautious use of intravenous fluids</td>
<td>Empirical antibiotics (third-generation cephalosporin and macrolide)</td>
</tr>
<tr>
<td>Intense education and optimum care of patients who have sickle cell anemia and asthma</td>
<td>Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)</td>
</tr>
<tr>
<td>Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)</td>
<td>Bronchodilators and steroids for patients with asthma</td>
</tr>
</tbody>
</table>

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*Figure 462-4* Probable pulmonary infarction in a 15 yr old patient with Hb-SS. A, Frontal radiograph shows consolidation and a small pleural effusion posteriorly in the right lower lobe. B, Radiograph obtained <24 hr later shows massive right middle and lower lobe consolidation and effusion. No organisms could be cultured. The diagnosis of “probably pulmonary infarction” was established clinically. (Courtesy of Dr. Thomas L. Stovis, Children’s Hospital of Michigan, Detroit, MI. From Kuhn JP, Slowis TL, Haller JO: Caffey’s pediatric diagnostic imaging, vol 1, ed 10, Philadelphia, 2004, Mosby, p. 1087.)
hematuria, proteinuria, renal insufficiency, concentrating defects, or hypertension.

The common presence of nocturnal enuresis occurring in children with sickle cell anemia is not well defined but is troublesome to affected children and their parents. The overall prevalence of enuresis was 33% in the Cooperative Study of Sickle Cell Disease with the highest prevalence (42%) among children ages 6-8 yr. Furthermore, enuresis may still occur in approximately 9% of the older adolescent group. As would be the case in all children with nocturnal enuresis, we would systematically evaluate the children for recurrent urinary tract infections, kidney function, and possibly obstructive sleep apnea syndrome with a supportive history. Unfortunately, most children with nocturnal enuresis do not have an etiology and targeted therapeutic interventions have been of limited success.

**Cognitive and Psychological Complications**

As with any child with a chronic illness, good health maintenance must include routine psychological and social assessment. Ongoing evaluation of the family unit and identification of the resources available to cope with a chronic illness are critical for optimal management. Children and adolescents with sickle cell disease also have decreased quality of life, as measured on standardized assessments, compared to their siblings and children with other chronic diseases. Furthermore, children with sickle cell disease are at great risk for academic failure and have a 20% high school graduation rate. One reason behind the low high school graduation rate is that approximately a third of children with sickle cell anemia have had a cerebral infarct—either silent cerebral infarcts or overt strokes. Children with cerebral infarcts require ongoing cognitive and school performance assessment so that education resources can be focused to optimize educational attainment. Relevant support groups and attendance in group activities, such as camps for children with sickle cell disease, may be of direct benefit by improving self-esteem and establishing peer relationships.

**Other Complications**

In addition to the previously mentioned organ dysfunctions, patients with sickle cell anemia can have other significant complications. These complications include, but are not limited to sickle cell retinopathy, delayed onset of puberty, and leg ulcers. Optimal treatment for each of these entities has not been determined and individual management requires consultation with the disease-specific specialist, a hematologist, and primary care physician.

**THERAPEUTIC CONSIDERATIONS**

**Hydroxyurea**

Hydroxyurea, a myelosuppressive agent, is the only drug proven effective in reducing the frequency of painful episodes. In a large clinical trial of adults with sickle cell anemia, hydroxyurea was found to decrease the rate of hospitalization for painful episodes by 50% and the rate of ACS and blood transfusion by almost 50%. Follow-up of the original trial found that adults taking hydroxyurea had shorter hospital stays and required less pain medication during hospitalization. In children with sickle cell anemia, a safety feasibility trial of hydroxyurea demonstrated that hydroxyurea was safe and well tolerated in children >5 yr of age. No clinical adverse events were identified in this study; the primary toxicities were limited to myelosuppression that reversed upon cessation of the drug. Infants treated with hydroxyurea also experienced fewer episodes of pain, dactylitis, and ACS, and were less-often hospitalized or received a blood transfusion. Despite being a myelosuppressive agent, the infants treated with hydroxyurea did not experience increased rates of bacteremia or serious infection.

Hydroxyurea may be indicated for other sickle cell–related complications, especially in patients who are unable to tolerate other treatments. For patients who either will not or cannot continue blood transfusion therapy to prevent recurrent stroke, hydroxyurea therapy may be a reasonable alternative. The trial assessing the efficacy of hydroxyurea as an alternative to transfusions to prevent second stroke was terminated early after the data safety and monitoring found an increased stroke rate in the hydroxyurea arm compared to the transfusion arm (0 vs. 7 [10%]). Hydroxyurea alone is inferior to transfusion therapy for secondary stroke prevention in patients who do not have contraindications to ongoing transfusions. Although not investigated as a primary outcome, hydroxyurea appears to have promise for the prevention of recurrent priapism. One study found hydroxyurea decreased glomerular hyperfiltration in young children with sickle cell anemia.

The long-term toxicity associated with initiating hydroxyurea in very young children has not yet been established. However, all evidence to date suggests that the benefits far outweigh the risks. For these reasons, children >2 yr of age receiving hydroxyurea require well-informed parents and medical care by pediatric hematologists, or at least co-management by a physician with expertise in immunosuppressive medications. The typical starting dose of hydroxyurea is 15–20 mg/kg given once daily, with an incremental dosage increase every 8 wk of 5 mg/kg, and if no toxicities occur, up to a maximum of 35 mg/kg per dose. The infant hydroxyurea study found young children could safely be started at 20 mg/kg/day without increased toxicity. Achievement of the therapeutic effect of hydroxyurea can require several months, and for this reason, inpatient initiating of hydroxyurea is not optimal. We prefer to introduce the concept to parents within the first year of life, provide literature that describes both the pros and cons of starting hydroxyurea in children with severe symptoms of sickle cell disease, and educate parents on starting hydroxyurea in asymptomatic children as a preventative therapy for repetitive pain and ACS events. Other effects of hydroxyurea that may vary include an increase in the total hemoglobin level and a decrease in the TCD velocity.

**Hematopoietic Stem Cell Transplantation**

The only cure for sickle cell anemia is transplantation with human leukocyte antigen (HLA)—matched hematopoietic stem cells from a sibling or unrelated donor. The most common indications for transplant are recurrent ACS, stroke and abnormal TCD. Sibling-matched stem cell transplantation has a lower risk for graft-versus-host disease than unrelated donors. However, few children have suitable sibling donors. Stem cell transplantation using an unrelated but well-matched donor is the subject of an open clinical trial. The decision to consider unrelated transplantation should involve appropriate consultation and counseling from physicians with expertise in sickle cell transplantation.

Stem cell transplantation for children with sickle cell disease with a genetically matched sibling is not routinely done, in part because of the known risk of transplantation-related mortality and morbidity in a short period of time, commonly less than 2 yr after the transplantation versus the high probability that patients will live to and through adulthood. The use of hydroxyurea has dramatically decreased the disease burden for the patient and family, with associated far fewer hospitalizations for pain or ACS episodes and less use of blood transfusions. Furthermore, the field of stem cell transplantation is progressing so rapidly that in a decade or less haplo-identical transplantation will be considered a viable option for not only individuals with severe disease, but also those with less-severe manifestations. Haplo-identical transplantations in adults with severe manifestations of sickle cell disease resulted in no deaths, and approximately 60% of the participants were cured of the disease. Low intensity, nonmyeloablative HLA-matched sibling allogenic stem cell transplantation has been employed in patients ≥16 years of age.

**Red Blood Cell Transfusions**

Red blood cell transfusions are frequently used in the management of children with sickle cell anemia, both in the treatment of acute complications such as ACS, aplastic crisis, splenic sequestration, and acute stroke, and to prevent surgery-related ACS and first stroke in patients with abnormal TCD or MRI findings (silent stroke). Patients with sickle cell disease are at increased risk of developing alloantibodies to less-common red cell surface antigens after receiving even a single transfusion. In addition to standard cross-matching for major blood group antigens (A, B, O, RhD), more extended matching should be performed to identify donor units that are C-, E-, and Kell-antigen.
negative. Some centers have begun to perform full red blood cell phenotyping for patients receiving chronic blood transfusions.

Three methods of blood transfusion therapy are used in the management of acute and chronic complications associated with sickle cell anemia: automated erythrocytapheresis, manual exchange transfusion (phlebotomy of a set amount of patient's blood followed by rapid administration of donated packed red blood cells), and simple transfusion. Automated erythrocytapheresis is the preferred method for patients requiring chronic blood transfusion therapy because there is a minimum net iron balance after the procedure, followed by manual exchange transfusion. Simple transfusion therapy is the least-preferable method for regular blood transfusion therapy because this strategy results in the highest net-positive iron balance after the procedure. Despite being the preferred method, erythrocytapheresis is less-frequently performed because of the requirement of technical expertise, large venous access, multiple units of matched red blood cells, and an available cytapheresis machine.

**Preparation for surgery** for children with sickle cell disease requires a coordinated effort between the hematologist, surgeon, and primary care provider. ACS and pain are the 2 most common postoperative complications, with ACS being a significant risk factor for postoperative death. Blood transfusion prior to surgery for children with sickle cell anemia is recommended to raise the hemoglobin level preoperatively to no more than 10 g/dL, although benefit also may be seen at lower hemoglobin values. The rate of serious complications, including a higher rate of ACS in patients who do not receive blood transfusion when compared to those who do. When available, blood transfusion therapy prior to surgery should be the standard approach. When preparing a child with sickle cell anemia for surgery with a simple blood transfusion, caution must be used not to elevate the hemoglobin beyond 10 g/dL because of the risk of hyperviscosity syndrome. For children with sickle cell anemia, exchange transfusion prior to surgery is of no greater benefit than simple blood transfusion and carries significantly higher risk of red blood cell alloimmunization. For children with milder forms of sickle cell disease, such as HbSC or HbSβ-thalassemia, a decision must be made on a case-by-case basis as to whether an exchange transfusion is warranted, because a simple transfusion may raise the hemoglobin to an unacceptable level.

**Excessive Iron Stores**
The primary toxic effect of blood transfusion therapy relates to excessive iron stores, which can result in organ damage and premature death. Excessive iron stores develop after 100 mL/kg of red cell transfusion or about 10 transfusions. The assessment of iron overload in children receiving regular blood transfusions is difficult. The most commonly used and least-invasive method of estimating total-body iron involves serum ferritin levels. Ferritin measurements have significant limitations in their ability to estimate iron stores for several reasons, including, but not limited to, elevation during acute inflammation and poor correlation with excessive iron in specific organs after 2 yr of regular blood transfusion therapy. Advances in technology have improved the assessment of iron stores among children with sickle cell disease receiving regular blood transfusion therapy. MRI of the liver has proven to be the most effective and common approach for assessment of iron stores. The imaging strategy is more accurate than serum ferritin in measuring heart and liver iron content. MRI T2⁎ and MRI R2 and R2⁎ sequences are now being used to estimate iron levels in the heart and liver. The standard for iron assessment previously was biopsy of the liver, which is an invasive procedure exposing children to the risk of general anesthesia, bleeding, and pain. Liver biopsy alone does not accurately estimate total-body iron, as iron deposition in the liver is not homogenous and varies among the affected organs; that is, the amount of iron found in the liver is not equivalent to cardiac tissues. The major advantage of a liver biopsy is that histologic assessment of the parenchyma can be ascertained along with appropriate staging of suspected pathology, particularly cirrhosis.

The primary treatment of excessive iron stores resulting from red blood cell transfusion requires iron chelation using medical therapy. In the United States, 3 chelating agents are commercially available and approved for use in transfusional iron overload. Deferoxamine is administered subcutaneously 5 of 7 nights/wk for 10 hr a night. Deferasirox is an effervescent tablet that is dissolved in liquid and taken by mouth daily, and deferiprone is available in tablets taken orally twice a day. The FDA approved deferasirox, the newest orally administered chelator, in 2005 for use in patients age ≥2 yr. Deferiprone is an older oral chelator that has been widely used outside of the United States for many years and was approved by the FDA in 2011, but requires weekly monitoring of complete blood counts because of a risk of neutropenia throughout therapy. Transfusion-related excessive iron stores in children with sickle cell disease should be managed by a physician with expertise in chelation therapy owing to the risk of significant toxicity from available chelation therapies.

**OTHER SICKLE CELL SYNDROMES**
The most commonly occurring sickle cell syndromes besides HbSS are HbSC, HbSβ-thalassemia zero, and HbSβ-thalassemia+. The other syndromes—HbSD, HbSQV, HbS HPFH, and other variants—are much less common. Patients with HbSβ-thalassemia zero have a clinical phenotype similar to those with HbSS. HbSC does not polymerize like HbSS, but crystals of HbC interact with membrane ion transport, dehydrating red cells and inducing sickling. Children who have HbSC disease can experience the same symptoms and complications as those with severe HbSS disease, but the frequency of such experience is less. Children with HbSC also have increased incidence of retinopathy, chronic hypersplenism, splenic sequestration, and renal medullary carcinoma. The natural history of the other sickle cell syndromes is variable and difficult to predict because of the lack of systematic evaluation.

There is no validated model that can predict the clinical course of an individual with sickle cell disease. A patient with HbSC can have a more-severe clinical course than a patient with HbSS. Management of end-organ dysfunction in children with sickle cell syndromes requires the same general principles as managing patients with sickle cell anemia; however, each situation should be managed on a case-by-case basis and requires consultation with a pediatric hematologist.

**ANTICIPATORY GUIDANCE**
The 2 primary goals of pediatric care are to promote health and prevent disease. Children with sickle cell disease should receive general health maintenance as recommended for all children with special attention to the following disease specific guidance.

**Spleen Palpation**
Splenomegaly is a common complication of sickle cell anemia and splenic sequestration can be life-threatening. Parents and primary caregivers should be taught how to palpate the spleen to determine if the spleen is enlarging starting at the first visit with reinforcement at subsequent visits. Parents should also demonstrate spleen palpation to the provider.

**Prophylactic Penicillin**
Children with sickle cell anemia should receive prophylactic oral penicillin VK until at least 5 yr of age (125 mg twice a day up to age 3 yr, and then 250 mg twice a day thereafter). No established guidelines exist for penicillin prophylaxis beyond 5 yr of age, and some clinicians continue penicillin prophylaxis, whereas others recommend discontinuation. Continuation of penicillin prophylaxis should be continued beyond 5 yr of age in children with history of pneumococcal infection because of the increased risk of a recurrent infection. An alternative for children who are allergic to penicillin is erythromycin ethyl succinate 10 mg/kg twice a day.

**Immunizations**
In addition to penicillin prophylaxis, routine childhood immunizations, as well as the annual administration of influenza vaccine, are highly recommended. Children with sickle cell anemia develop functional asplenia and also require immunizations to protect against encapsulated organisms including additional pneumococcal and meningococcal vaccinations. Vaccination guidelines can be found at

Transcranial Doppler Ultrasound
Primary stroke prevention using TCD has resulted in a decrease in the prevalence of overt stroke among children with sickle cell anemia. Children with HbSS or HbSβ-thalassemia zero should be screened annually with TCD starting at age 2 yr. TCD is best performed when the child is quietly awake and in their usual state of health. TCD measurements may be falsely elevated in the setting of acute anemia or falsely low immediately after blood transfusions or if procedural sedation is used. Screening should occur annually from age 2-16 yr. Abnormal values should be repeated within 2-4 wk to identify patients at greatest risk of overt stroke. Conditional values should be repeated within 3 mo, and normal values repeated annually. Routine neuroimaging with MRI in asymptomatic patients is not currently recommended.

Hydroxyurea
Monitoring children on hydroxyurea is labor intensive. Hydroxyurea is a chemotherapeutic agent that requires the same level of nursing and physician oversight as any child with cancer receiving chemotherapy. The parents must be educated about the consequences of therapy, and when ill, children should be promptly evaluated. Complete blood count should be checked at least every 4 wk after initiation of therapy or any dose change to monitor for hematologic toxicity and then every 8 wk. Hydroxyurea should be temporarily discontinued and dose adjusted if the absolute neutrophil count falls below 2,000/µL or platelets fall below 80,000/µL. Hydroxyurea is a pregnancy class D medication and adolescents should be counseled regarding methods to prevent pregnancy while taking hydroxyurea. Close monitoring of the patient requires a commitment by the parents and patient, as well as diligence by a physician, to identify toxicity early.

Regular Blood Transfusion Therapy
At the initiation of blood transfusion therapy, children with sickle cell anemia should have testing to identify the presence of alloantibodies and red blood cell phenotyping, which is performed to identify the best matched blood. Children meeting criteria for chronic transfusion therapy should receive annual evaluation for transfusion transmitted infections including hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). After receiving 100 mg/kg of red blood cell transfusions, regular assessments of iron overload should begin; usually periodic measurements of serum ferritin. For children requiring chelation therapy, an audiogram should be performed annually, as well as monitoring for organ toxicity, including liver function tests and endocrine evaluation of pituitary dysfunction because of iron deposition.

Pulmonary and Asthma Screening
Pulmonary complications of sickle cell disease are common and life-threatening. Asthma is common particularly in African-American children. As would be the case in all children, good clinical practice necessitates evaluation for asthma symptoms and asthma risk factors in children with sickle cell disease, particularly in light of the insurmountable evidence that asthma is associated with increased rate of sickle cell disease morbidity and mortality. All children should receive annual screening for signs and symptoms of lower airway disease, such as nighttime cough and exercise-induced cough. In children with symptoms consistent with lower airway disease, consider consultation with an asthma specialist. Pulse oximetry readings should be performed during well visits to identify children with abnormally low daytime oxygen saturations. For children with snoring and daytime somnolence, and symptoms associated with obstructive sleep apnea syndrome, referral to a sleep specialist should be considered.

Retinopathy
Effective therapy for retinopathy associated with sickle cell disease exists. Patients at highest risk for the development of retinopathy should receive annual screening by an ophthalmologist to identify vascular changes that would benefit from laser therapy. Although changes may occur earlier, children with sickle cell disease should begin annual screening at age 10 yr.

Renal
Sickle cell–associated renal disease, starts in infancy and may not become clinically manifested until adulthood. Screening for early signs of sickle nephropathy using urinalysis to identify proteinuria is recommended with annual albumin:creatinine ratios. The age to begin screening for proteinuria has not been defined, but some experts recommend screening annually after at least 10 yr of age if not sooner. If the albumin:creatinine ratio is elevated (>30 mg/g), it should be repeated with an early morning urine collection, and if still elevated, the patient should be referred to a pediatric nephrologist. Males with sickle cell disease should also receive counseling regarding the diagnosis and treatment of priapism. Because of the high frequency of enuresis beyond early childhood, approximately 9% of adolescents between 18 and 20 yr of age, parents and caregivers should be educated about the prolonged nature of enuresis in this disease. As is the case in the general population, obstructive sleep apnea syndrome is associated with an increased prevalence of enuresis in sickle cell disease. Unfortunately, no evidence-based therapies have been developed to treat enuresis in children and young adults with sickle cell disease. In children with enuresis who have symptoms and clinical features of obstructive sleep apnea syndrome, referral to sleep specialists for evaluation is recommended.

Echocardiography
Echocardiography has gained popularity as a screening tool to identify individuals with sickle cell disease who have pulmonary artery hypertension. No evidence currently exists that children with sickle cell disease and elevated tricuspid jet velocity above 2.5 cm/sec have an increased rate of mortality. Subsequent studies in adults with sickle cell disease have found the echocardiography to be insensitive at identifying individuals truly at risk for pulmonary hypertension, although an elevated tricuspid velocity measurement may still be a risk factor for premature death in adults with sickle cell disease. The current recommendation is to refer those with severe cardiopulmonary symptoms from associated pulmonary artery hypertension to pediatric cardiologist for a more formal evaluation.

Bibliography is available at Expert Consult.

462.2 Sickle Cell Trait (Hemoglobin AS)
Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

The prevalence of sickle cell trait varies throughout the world; in the United States, the incidence is 7-10% of African-Americans. Because all state newborn screening programs include sickle cell disease, for most children, sickle cell trait is first identified on their newborn screen. Communication of sickle cell trait status from infancy to young adulthood for the affected individual, family, and healthcare providers is often inconsistent and many young adults are unaware of their sickle cell trait status.

The production of HbS is influenced by the number of α-thalassemia genes present, and the amount of HbS. By definition among individuals with sickle cell trait, the HbS level is <50%. The life span of people with sickle cell trait is normal, and serious complications are extremely rare. The CBC is within the normal range (Fig. 462-5B). Hemoglobin analysis is diagnostic, revealing a predominance of HbA, typically >50%, and HbS <50%. Rare complications of sickle cell trait are associated with sudden death during rigorous exercise, splenic infarction at high altitude, hematuria, hyponatremia, deep vein thrombosis, and susceptibility to eye injury with formation of a hyphema (Table 462-5). Renal
Bibliography


Diseases of the Blood

Table 462-5 Complications Associated with Sickle Cell Trait

<table>
<thead>
<tr>
<th>DEFINITE ASSOCIATIONS</th>
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<tbody>
<tr>
<td>Renal medullary cancer</td>
</tr>
<tr>
<td>Hematuria</td>
</tr>
<tr>
<td>Renal papillary necrosis</td>
</tr>
<tr>
<td>Hyposthenuria</td>
</tr>
<tr>
<td>Splenic infarction</td>
</tr>
<tr>
<td>Exertional rhabdomyolysis</td>
</tr>
<tr>
<td>Exercise-related sudden death</td>
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<tr>
<td>Protection against severe falciparum malaria</td>
</tr>
<tr>
<td>Microalbuminuria (adults)</td>
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</tbody>
</table>


medullary carcinoma is also associated with sickle cell trait and occurs predominantly in young adults and children.

Children with sickle cell trait do not require limitations on physical activities. Sudden death in persons with sickle cell trait while exercising under extreme conditions is most likely associated with a second genetic factor and/or environmental factors, and not the presence of sickle cell trait itself. No causal pathway has been implicated for the presence of sickle cell trait and sudden death. All patients with sickle cell trait who participate in rigorous athletic activities should receive maximum hydration and appropriate rest during exertion, as would be the precautionary steps for all athletes, particularly when participating in hot humid conditions. The presence of sickle cell trait should never be a reason to exclude a person from athletic participation but rather should serve as an indication that prudent surveillance is necessary to ensure appropriate hydration and prevention of exhaustion from heat or other strenuous exercise. If athletes are to be screened for sickle cell trait, then appropriate genetic counseling should be provided, along with the knowledge that genetic information may provide opportunities to challenge paternity. Such situations are typically handled by a pediatrician or hematologist accustomed to providing both a balanced approach to genetic counseling and addressing the challenges about paternity.

462.3 Other Hemoglobinopathies

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

HEMOGLOBIN C

The mutation for HbC is at the same site as HbS, with substitution of lysine instead of valine for glutamine. In the United States, hemoglobin C trait (HbAC) occurs in 1:40 and homozygous
Abnormal hemoglobin C disease (HbCC) occurs in 1 : 5,000 African-Americans. HbAC is asymptomatic. HbCC can result in mild anemia, splenomegaly, and choledolithiasis; rare cases of spontaneous splenic rupture have been reported. Sickling does not occur. This condition is usually diagnosed through newborn screening programs. HbC crystallizes, disrupting the red cell membrane, and HbC crystals may be visible on peripheral smear (see Fig. 462-5C).

**HEMOGLOBIN E**

HbE is an abnormal hemoglobin resulting from a qualitative mutation in the β-globin gene and is the second most common global mutation worldwide. Patients may have asymptomatic hemoglobin E trait (HbAE) or benign homozygous hemoglobin E disease (HbEE). Compound heterozygous hemoglobin E/β-thalassemia produces clinical phenotypes ranging from moderate to severe anemia depending on the β-thalassemia mutation. In California, HbE/β-thalassemia is found almost exclusively in persons of Southeast Asian descent, with a prevalence of 1 : 2,600 births.

**HEMOGLOBIN D**

At least 16 variants of HbD exist. HbD-Punjab (Los Angeles) is a rare hemoglobin that is seen in 1-3% of Western Indians and in some Europeans with Asian-Indian ancestry and produces symptoms of sickle cell disease when present in combination with HbS. Heterozygous HbD or hemoglobin D trait (HbAD) is clinically silent. Heterozygous HbDD or HbD disease produces a mild to moderate anemia with splenomegaly.

**462.4 Unstable Hemoglobin Disorders**

*Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky*

At least 200 rare unstable hemoglobins have been identified; the most common is Hb Köln. Most patients seem to have de novo mutations rather than inherited hemoglobin disorders. The best studied unstable hemoglobins are the ones leading to hemoglobin denaturation from mutations affecting heme binding. The denatured hemoglobin can be visualized during severe hemolysis or after splenectomy as Heinz bodies. Unlike the Heinz bodies seen after toxic exposure, in unstable hemoglobins, Heinz bodies are present in reticulocytes and older red cells (see Fig. 462-5D). Heterozygotes are asymptomatic.

Children with homozygous gene mutations can present in early childhood with anemia and splenomegaly or with unexplained hemolytic anemia. Hemolysis is increased with febrile illness and with the ingestion of oxidant medications (similar to glucose-6-phosphate dehydrogenase [G6PD] deficiency) with some unstable hemoglobins. If the spleen is functional, the blood smear can appear almost normal or have only hypochromasia and basophilic stippling. A diagnosis may be made by demonstrating Heinz bodies, hemoglobin instability, or an abnormal hemoglobin analysis (although some unstable hemoglobins have normal mobility and are not detected on hemoglobin analysis).

Treatment is supportive. Transfusion may be required during hemolytic episodes in severe cases. Oxidative drugs should be avoided, and folate supplementation may be helpful if dietary deficiency is a concern. Splenectomy may be considered in patients requiring recurrent transfusion or demonstrating poor growth, but the complications of splenectomy, including bacterial sepsis, risk of thrombosis, and the possibility of developing pulmonary hypertension, should be considered before surgery.

**462.5 Abnormal Hemoglobins with Increased Oxygen Affinity**

*Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky*

More than 110 high-affinity hemoglobins have been characterized. These mutations affect the state of hemoglobin configuration during oxygenation and deoxygenation. Hemoglobin changes structure when in the oxygenated versus the deoxygenated state. The deoxygenated state is termed the T (tense) state and is stabilized by 2,3-diphosphoglycerate. When fully oxygenated, hemoglobin assumes the R (relaxed) state. The exact molecular interactions between these 2 states are unknown. High-affinity hemoglobins contain mutations that either stabilize the R form or destabilize the T form. The interactions between the R and T forms are complex, and the mechanisms of the mutations are not known. In most cases, the high-affinity hemoglobins can be identified by hemoglobin analysis; approximately 20% must be characterized under controlled conditions where measurements are obtained with the P50 lowered to 9-21 mm Hg (normal: 23-29 mm Hg). The decreased P50 in these hemoglobin leads to an erythrocytosis with hemoglobin levels of 17-20 g/dL. Levels of erythropoietin and 2,3-diphosphoglycerate are normal. Patients are usually asymptomatic and do not need phlebotomy. If phlebotomy is performed, oxygen delivery could be problematic owing to the reduced number of hemoglobin molecules to carry oxygen.

**462.6 Abnormal Hemoglobins Causing Cyanosis**

*Michael R. DeBaun, Allison Grimes, Melissa J. Frei-Jones, and Elliott P. Vichinsky*

Abnormal hemoglobins causing cyanosis, also called structural met-hemoglobinemias, are rare. They are referred to as “M-hemoglobins” and represent a group of hemoglobin variants which result from point mutations in one of the globin chains, α, β, or γ located in the heme pocket. Thirteen known variants exist. These unstable hemoglobins lead to hemolytic anemia, most pronounced when the β-globin gene is affected. Clinically, these children are cyanotic from birth, without other signs or symptoms of disease, if the mutation is in the α-globin gene (HbM Boston, HbM Iwate, Hb Auckland). Infants with β-globin mutations become cyanotic later in infancy after the fetal hemoglobin switch (HbM Saskatoon, HbM Chile, HbM Milwaukee 1 and 2). γ-Chain mutations (HbF-M Fort Ripley, HbF-M Osaka, HbF Cincinnati, HbF Circleville, HbF Toms River, HbF Visceu) are all transient, presenting with cyanosis at birth, which resolves during the neonatal period after HbF production discontinues. The abnormal M hemoglobins exhibit autosomal dominant inheritance and are diagnosed by hemoglobin analysis. HbM variants may be not be isolated reliably using hemoglobin analysis (HPLC or isoelectric focusing [IEF]), consequently diagnostic confirmation may require DNA sequencing or mass spectrometry. There is no specific treatment and affected patients do not respond to treatments used for enzyme-deficient met-hemoglobininaemia. Beyond cyanosis, individuals are otherwise asymptomatic and do not require additional monitoring. Children with the β-globin form should avoid oxidant drugs. Individuals with all forms have a normal life expectancy and pregnancy course.

Low-affinity hemoglobins have less cyanosis than the M hemoglobins. The amino acid substitutions destabilize the oxyhemoglobin and lead to decreased oxygen saturation. The best characterized are Hb Kansas, Hb Beth Israel, and Hb Denver. Hemoglobin analysis (IEF and HPLC techniques) may be normal in affected individuals. When clinically suspected, oxygen affinity studies reveal a right-shifted dissociation curve and heat testing demonstrates unstable hemoglobin. Children present with mild cyanosis only.

**462.7 Hereditary Methemoglobinemia**

*Michael R. DeBaun, Allison Grimes, Melissa J. Frei-Jones, and Elliott P. Vichinsky*

Hereditary methemoglobinemia is a clinical syndrome caused by an increase in the serum concentration of methemoglobin either as a result of congenital changes in hemoglobin synthesis or of metabolism...
leading to imbalances in reduction and oxidation of hemoglobin. The iron molecule in hemoglobin is normally in the ferrous state (Fe\(^{2+}\)), which is essential for oxygen transport. Under physiologic conditions there is a slow, constant loss of electrons to released oxygen, and the ferric (Fe\(^{3+}\)) form combines with water, producing methemoglobin (MetHb). The newly formed MetHb has a reduced ability to bind oxygen.

Two pathways for MetHb reduction exist. The physiologic and predominant pathway is a reduced form of nicotinamide adenine dinucleotide (NADH)-dependent reaction catalyzed by cytochrome b5 reductase. This mechanism is >100-fold more efficient than the production of MetHb. The alternate pathway utilizes nicotinamide adenine dinucleotide phosphate generated by G6PD in the hexose monophosphate shunt and requires an extrinsic electron acceptor to be activated (i.e., methylene blue, ascorbic acid, riboflavin). In normal individuals, oxidation of hemoglobin to MetHb occurs at a slow rate, 0.5-3%, which is countered by MetHb reduction to maintain a steady state of 1% MetHb.

MetHb may be increased in the red cell owing to exposure to toxic substances or to absence of reductive pathways, such as NADH-cytochrome b5 reductase deficiency. Toxic methemoglobinemia is much more common than hereditary methemoglobinemia (Table 462-6). Infants are exceptionally vulnerable to hemoglobin oxidation because their erythrocytes have half the amount of cytochrome b5, which is essential for oxygen transport. Under physiologic conditions in which there is a slow, constant loss of electrons to released oxygen, the ferric (Fe\(^{3+}\)) form combines with water, producing methemoglobin (MetHb). The newly formed MetHb has a reduced ability to bind oxygen.

Table 462-6  Known Etiologies of Acquired Methemoglobinemia

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Benzocaine</td>
<td></td>
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<tr>
<td>Chloroquine</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td></td>
</tr>
<tr>
<td>EMLA (eutectic mixture of local anesthetics) topical anesthetic</td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td></td>
</tr>
<tr>
<td>Phenazopyridine</td>
<td></td>
</tr>
<tr>
<td>Prilocaine</td>
<td></td>
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<tr>
<td>Primaquine</td>
<td></td>
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<tr>
<td>Riluzole</td>
<td></td>
</tr>
<tr>
<td>Silver nitrate</td>
<td></td>
</tr>
<tr>
<td>Sodium nitrate</td>
<td></td>
</tr>
<tr>
<td>Sulfinamides</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>MEDICAL CONDITIONS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric gastrointestinal infection, sepsis</td>
<td></td>
</tr>
<tr>
<td>Recreational drug overdose with amyl nitrate (“poppers”)</td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease–related painful episode</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MISCELLANEOUS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aniline dyes</td>
<td></td>
</tr>
<tr>
<td>Fume inhalation (automobile exhaust, burning of wood and plastics)</td>
<td></td>
</tr>
<tr>
<td>Herbicides</td>
<td></td>
</tr>
<tr>
<td>Industrial chemicals: nitrobenzene, nitroethane (found in nail polish, resins, rubber adhesives)</td>
<td></td>
</tr>
<tr>
<td>Pesticides</td>
<td></td>
</tr>
<tr>
<td>Gasoline octane booster</td>
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</tbody>
</table>


The first reported inherited disorder causing methemoglobinemia resulted from an enzymatic deficiency of NADH cytochrome b5 reductase, which was classified into 2 distinct phenotypes. In type I, the most common form, the deficiency of NADH cytochrome b5 activity is found only in erythrocytes, with other cell types unaffected. In type II, the enzyme deficiency is present in all tissues and results in more significant symptoms beginning in infancy with encephalopathy, mental retardation, spasticity, microcephaly, and growth retardation with death most often by 2 yr of age. Both types exhibit an autosomal recessive inheritance pattern.

Clinically, cyanosis varies in intensity with season and diet. The time of cyanosis onset also varies; in some patients it appears at birth, in others as late as adolescence. Although as much as 50% of the total circulating hemoglobin may be in the form of nonfunctional MetHb, little or no cardiorespiratory distress occurs in these patients, except on exertion.

Daily oral treatment with ascorbic acid (200-500 mg/day in divided doses) gradually reduces the MetHb to approximately 10% of the total.
pigment and alleviates the cyanosis as long as therapy is continued. Chronic high doses of ascorbic acid have been associated with hyperoxaluria and renal stone formation. Ascorbic acid should not be used to treat toxic methemoglobinemia. When immediately available, poison control should be contacted to verify the most up-to-date therapeutic strategies. Like ascorbic acid, riboflavin utilizes the alternate pathway of MetHb reduction and is most effective when given in high doses (400 mg once daily). Methylene blue, administered intravenously (1-2 mg/kg initially), is used to treat toxic methemoglobinemia. An oral dose can be administered (100-300 mg PO per day) as maintenance therapy.

Methylene blue should not be used in patients with G6PD deficiency. This treatment is ineffective and can cause severe oxidative hemolysis. In the event that methylene blue is given to a patient with G6PD deficiency, there will be no improvement in symptoms and marked hemolysis has been reported within 24 hr of administration. Because G6PD deficiency status is rarely known at the time of treatment, a careful history should be elicited. When the history is negative for symptoms of G6PD deficiency, treatment with methylene blue should be initiated judiciously, and the patient should be closely monitored for improvement.

462.9 Syndromes of Hereditary Persistence of Fetal Hemoglobin
Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

HPFH syndromes are a form of thalassemia; mutations are associated with a decrease in the production of either or both β- and δ-globins. There is an imbalance in the α-non-α synthetic ratio (see Chapter 462.9) characteristic of thalassemia. More than 20 variants of HPFH have been described. They are deletional, δβ0 (Black, Ghanaian, Italian), nondeletional (Tunisian, Japanese, Australian), linked to the β-globin–gene cluster (British, Italian-Chinese, Black), or unlinked to the β-globin–gene cluster (Atlanta, Czech, Seattle). The δβ0 forms have deletions of the entire δ- and β-globin gene sequences, and the most common form in the United States is the Black (HPFH 1) variant. As a result of the δ and β gene deletions, there is production only of γ-globin and formation of HbF. In the homozygous form, no manifestations of thalassemia are present. There is only HbF with very mild anemia and slight microcytosis. When inherited with other variant hemoglobins, HbF is elevated into the 20-30% range; when inherited with HbS, there is an amelioration of sickle cell disease with fewer complications.

462.10 Thalassemia Syndromes
Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

Thalassemia refers to a group of genetic disorders of globin chain production in which there is an imbalance between the α-globin and β-globin chain production. β-Thalassemia syndromes result from a decrease in β-globin chains, which results in a relative excess of α-globin chains. β+ -Thalassemia refers to the absence of production of the β-globin. When patients are homozygous for the β-thalassemia gene, they cannot make any normal β chains (HbA). β−-Thalassemia indicates a mutation that makes decreased amounts of normal β-globin, but it is still present (HbA). β−-Thalassemia syndromes are more severe than β−-thalassemia syndromes, but there is significant variability between the genotype and phenotype. β-Thalassemia major refers to the severe β-thalassemia patient who requires early transfusion therapy and often is homozygous for β0 mutations. β+ -Thalassemia intermedia is a clinical diagnosis of a patient with a less-severe clinical phenotype that usually does not require transfusion therapy in childhood. Many of these patients have at least 1 β−-thalassemia mutation. β-Thalassemia syndromes usually require a β-thalassemia mutation in both β-globin genes. Carriers with a single β-globin mutation are generally asymptomatic, except for microcytosis and mild anemia. In α-thalassemia, there is an absence or reduction in α-globin production. Normal individuals have 4 α-globin genes. The more genes affected, the more severe the disease. An α−-mutation indicates no α-chains produced from that gene. An α+ mutation produces a decreased amount of α-globin chain. The primary pathology in the thalassemia syndromes stems from the quantity of globin produced, whereas the primary pathology in sickle cell disease is related to the quality of β-globin produced.

Epidemiology
There are >200 different mutations resulting in absent or decreased globin production. Although most are rare, the 20 most common abnormal alleles constitute 80% of the known thalassemias worldwide; 3% of the world’s population carries alleles for β-thalassemia, and in Southeast Asia 5-10% of the population carry alleles for α-thalassemia. In a particular region, there are fewer common alleles. In the United States, an estimated 2,000 persons have β-thalassemia major.

Pathophysiology
Two related features contribute to the sequelae of β-thalassemia major: inadequate β-globin gene production leading to decreased levels of normal hemoglobin (HbA) and unbalanced α- and β-globin chain production. In β-thalassemia major, α-globin chains are in excess to non-α-globin chains, and α-globin tetramers (α4) are formed and appear as red cell inclusions. The free α-globin chains and inclusions are very unstable, precipitate in red cell precursors, damage the red cell membrane, and shorten red cell survival leading to anemia and increased erythroid production. Table 462-7 shows selected features of thalassemia. This results in a marked increase in erythropoiesis with early erythroid precursor death in the bone marrow. Clinically, this is characterized by a lack of maturation of erythrocytes and an inappropriately low reticulocyte count. This ineffective erythropoiesis and the compensatory massive marrow expansion with erythroid hyperactivity characterize β-thalassemia. Because the β5-thalassemia patient cannot make HbA, the α-chains combine with γ-chains, resulting in HbF (α2γ2) being the dominant hemoglobin. In addition to the natural survival effect, the γ-globin chains may be produced in increased amounts, which is regulated by genetic polymorphisms. δ-Chain synthesis is not usually affected in β-thalassemia or β-thalassemia trait, and, therefore, patients have a relative or absolute increase in HbA, production (αδ2).

In the α-thalassemia syndromes, 2 genes with 2 maternal and 2 paternal alleles control α-globin production, which varies from complete absence (hydrops fetalis) to only slightly reduced (α-thalassemia silent carrier). In the α-thalassemia syndromes, an excess of β- and γ-globin chains are produced. These excess chains form Bart hemoglobin (γγ) in fetal life and HbH (ββ) after birth. These abnormal tetramers are nonfunctional hemoglobins with very high oxygen affinity. They do not transport oxygen and result in extravascular hemolysis. A fetus with the most severe form of α-thalassemia (hydrops fetalis) develops in utero anemia and fetal loss because HbF production requires sufficient amounts of α-globin. In contrast, infants with β-thalassemia major become symptomatic only after birth when HbA predominates and insufficient β-globin production manifests in clinical symptoms.

Homozygous β-thalassemia (thalassemia major, Cooley anemia)
Clinical Manifestations
If not treated, children with homozygous β-thalassemia usually become symptomatic from progressive hemolytic anemia, with profound weakness and cardiac decompensation during the 2nd 6 mo of life. Depending on the mutation and degree of fetal hemoglobin production, transfusions in β-thalassemia major are necessary beginning in the 2nd mo to 2nd yr of life, but rarely later. The decision to transfuse is multifactorial but is not determined solely by the degree of anemia. The developing signs of ineffective erythropoiesis such as growth
failure, bone deformities secondary to narrow expansion, hepatosplenomegaly are important variables in determining transfusion initiation.

The classic presentation of children with severe disease includes thalassemic facies (maxilla hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fractures, marked hepatosplenomegaly, and cachexia and is now primarily seen in countries without access to chronic transfusion therapy. Occasionally, patients with moderate anemia develop these features because of severe compensatory ineffective erythropoiesis.

In nontransfused patients with severe ineffective erythropoiesis, marked splenomegaly can develop with hypersplenism and abdominal symptoms. The features of ineffective erythropoiesis include expanded medullary spaces (with massive expansion of the marrow of the face and skull producing the characteristic thalassemic facies), extramedullary hematopoiesis, and higher metabolic needs (Fig. 462-7). The chronic anemia without transfusion exposure produces an increase in iron absorption from the gastrointestinal tract and secondary hemosiderosis-induced organ injury.

Chronic transfusion therapy dramatically improves the quality of life and reduces the complications of severe thalassemia. Transfusion-induced hemosiderosis becomes the major clinical complication of transfusion-dependent thalassemia. Each mL of packed red cells contains 1 mg of iron. Physiologically, there is no mechanism to eliminate excess body iron. Iron is initially deposited in the liver. Liver hemosiderosis develops after 1 yr of chronic transfusion therapy and is followed by iron deposition in the endocrine system. This leads to a high rate of hypothyroidism, hypogonadotrophic gonadism, growth hormone deficiency, hypoparathyroidism, and diabetes mellitus. After 10 yr of transfusion, cardiac dysfunction secondary to hemosiderosis begins. Eventually, most patients not receiving adequate iron chelation therapy die from cardiac failure and/or cardiac arrhythmias secondary to hemosiderosis. Hemosiderosis induced morbidity can be prevented by adequate iron chelation therapy.

### Laboratory Findings

In the United States, some children with β-thalassemia major will be identified on newborn screening as a result of the detection of only HbF on hemoglobin electrophoresis. However, the ethnicity and the mutations associated with transfusion-dependent thalassemia in the United States have dramatically changed. Many of the patients have diverse mutations, such as HbE thalassemia, which may not be identified or followed up by a newborn screening program. HbFE in the newborn may be a very common benign mutation caused by hemoglobin E/e in the United States. Standardized neonatal diagnosis of thalassemia disorders requires close follow-up of newborns with unclear thalassemia mutations and/or babies from high-risk ethnic groups.

Infants with serious β-thalassemia disorders have a progressive anemia after the newborn period. Microcytosis (MCV), hypochromia (MCH), and target cells characterize the red cells. Nucleated red cells, marked anisopoikilocytosis, and a relative reticulocytopenia are typically seen (see Fig. 462-5E). The hemoglobin level falls progressively to <6 g/dL unless transfusions are given. The reticulocyte count is

### Table 462-7 The Thalassemias

<table>
<thead>
<tr>
<th>THALASSEMIA</th>
<th>GLOBIN GENOTYPE</th>
<th>FEATURES</th>
<th>EXPRESSION</th>
<th>HEMOGLOBIN ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-THALASSEMIA</td>
<td>α−/α, α−/α</td>
<td>Normal</td>
<td>Normal</td>
<td>Newborn: Bart 1-2%</td>
</tr>
<tr>
<td>α-THALASSEMIA</td>
<td>α−/α−, α−/α−</td>
<td>Microcytosis, mild hypochromasia</td>
<td>Normal, mild anemia</td>
<td>Newborn: Bart 5-10%</td>
</tr>
<tr>
<td>β-THALASSEMIA</td>
<td>β−/β−</td>
<td>Variable microcytosis</td>
<td>Normal</td>
<td>Elevated A2, variable elevation of F</td>
</tr>
<tr>
<td>Silent</td>
<td>β−/β−, E/β</td>
<td>Microcytosis, nucleated RBC</td>
<td>Transfusion dependent</td>
<td>F 98% and A2 2%, E 30-40%</td>
</tr>
<tr>
<td>α−/α−, E/α−</td>
<td>Microcytosis, nucleated RBC</td>
<td>Transfusion dependent</td>
<td>F 70-95%, A2 2%, trace A</td>
<td></td>
</tr>
<tr>
<td>Dominant (rare)</td>
<td>A/A</td>
<td>Microcytosis, abnormal RBCs</td>
<td>Moderately severe anemia, splenomegaly</td>
<td>Elevated F and A2</td>
</tr>
<tr>
<td>δ-Thalassemia</td>
<td>A/A</td>
<td>Normal</td>
<td>Normal</td>
<td>A2 absent</td>
</tr>
<tr>
<td>(δβ)−-thalassemia</td>
<td>δ−/δ−, A/δ−</td>
<td>Hypochromia</td>
<td>Mild anemia</td>
<td>F 5-20%</td>
</tr>
<tr>
<td>Lepore</td>
<td>δ−/δ−, A/δ−</td>
<td>Microcytosis</td>
<td>Mild anemia</td>
<td>Lepore 8-20%</td>
</tr>
<tr>
<td>γδβ-Thalassemia</td>
<td>γδ−/γδ−, A/γ−</td>
<td>Microcytosis, hypochromia</td>
<td>Transfusion dependent</td>
<td>F 80%, Lepore 20%</td>
</tr>
<tr>
<td>γ-Thalassemia</td>
<td>γ−/γ−, A/γ−</td>
<td>Microcytosis, hypochromia</td>
<td>Thalassemia intermedia</td>
<td>Decreased F and A2</td>
</tr>
<tr>
<td>β-thalassemia</td>
<td>(βα)−, A/α−</td>
<td>Microcytosis</td>
<td>Moderate anemia, splenomegaly, thalassemia intermedia</td>
<td>Decreased F</td>
</tr>
<tr>
<td>HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN</td>
<td>Fe</td>
<td>Microcytosis, hypochromia</td>
<td>Insignificant unless homozygote</td>
<td>Decreased F</td>
</tr>
</tbody>
</table>

| Deletional | A/A | Microcytosis | Mild anemia | F 100% homozygotes |
| Nondeletional | A/A | Normal | Normal | F 20-40% |
Before initiating chronic transfusions, the diagnosis of transfusion dependent β-thalassemia should be confirmed by both clinical and laboratory parameters. β-Thalassemia major is a clinical diagnosis that requires the integration of laboratory findings and the clinical course. Of patients with homozygous β+-thalassemia (the most severe mutations), 15-20% may have a clinical course that is phenotypically consistent with thalassemia intermedia. In contrast, 25% of patients with homozygous β-thalassemia, typically a more benign genotype, may become transfusion-dependent thalassemia major. Transient clinical events, such as a sudden fall in hemoglobin secondary to an episode of parvovirus requiring transfusion, do not necessarily indicate the patient is a transfusion-dependent patient. The long-term observation of the clinical characteristics, such as growth, bony changes, and hemoglobin, are necessary to determine chronic transfusion therapy.

**Guidelines for Transfusion Therapy.** Patients at risk for transfusion therapy should have an extended red cell phenotype and/or genotype. Patients should receive red cells depleted of leukocytes and matched for, at least, D, C, c, E, e, and Kell antigens. Cytomegalovirus-negative units are indicated in stem cell transplantation candidates. Transfusions should generally be given at intervals of 3–4 wk, with the goal being to maintain a pretransfusion hemoglobin level of 9.5–10.5 g/dL. Ongoing monitoring for transfusion-associated transmitted infections (hepatitis A, hepatitis B, hepatitis C, HIV), alloimmunization, annual blood transfusion requirements, and transfusion reactions is essential.

### Iron Overload Monitoring

Excessive iron stores from transfusion cause many of the complications of β-thalassemia major. Accurate assessment of excessive iron stores is essential to optimal therapy. Serial serum ferritin levels are a useful screening technique in assessing iron balance trends, but results may not accurately predict quantitative iron stores. Undertreatment or overtreatment of presumed excessive iron stores can occur in managing a patient based on serum ferritin alone. Noninvasive measurement of quantitative organ injury is rapidly improving the treatment of iron overload. Quantitative measurement of liver iron and cardiac iron are standard and measurement of pancreatic and gonadal iron may be available soon. This technology, in collaboration with access to multiple chelators, will enable targeted chelation therapy for patients with organ specific hemosiderosis before the onset of overt organ failure. Available data suggests integration of these imaging technologies with chelation therapy may prevent heart failure, diabetes, and other pending organ dysfunction.

Quantitative liver iron by approved MRI technology is the best indicator of total-body iron stores and should be obtained in chronically transfused patients after chronic transfusion therapy has initiated. The liver iron results will help guide the chelation regimen. Quantitative cardiac iron, determined by T2* MRI cardiac software, should be obtained after 7 yr of transfusion therapy. It is not uncommon to have a discrepancy between the liver iron and the heart iron because of different rates of tissue loading and cardiac chelation efficacy.

### Chelation Therapy

Iron-chelation therapy should start as soon as the patient becomes significantly iron overloaded. In general, this occurs after 1 yr of transfusion therapy and correlates with the serum ferritin >1,000 ng/mL and/or a liver iron concentration of >2,500 μg/g dry weight. There are 3 available iron chelators (deferoxamine, deferasirox, and deferiprone); each varies in its route of administration, pharmacokinetics, adverse events, and efficacy. Many patients require combination chelation therapy at various points in their illness. The overall goal is to prevent hemosiderosis-induced tissue injury and avoid chelation toxicity. This requires close monitoring of the patients. In general, chelation toxicity increases as iron stores decrease. Deferoxamine (Desferal) is the most studied iron chelator; it has an excellent safety and efficacy profile. It requires subcutaneous, or intravenous, administration because of a half-life of less than 30 min, necessitating administration of at least 8 hr daily, 5-7 days/wk. Deferoxamine is initially started at 20 mg/kg and can be increased to 60 mg/kg in heavily iron-overloaded patients. The major problem with deferoxamine is noncompliance because of the route of administration.
Adverse side effects include ototoxicity, retinal changes, and bone dysplasia with truncal shortening.

The oral iron chelator deferasirox (Exjade) is commercially available in the United States. Of patients on Desferal, 70% have switched to deferasirox because it is orally available. Deferasirox has a half-life of more than 16 hr and requires once-a-day administration of a dispersible tablet in water. Initial dose is 20 mg/kg with gradual escalation to 30 mg/kg. The most common side effects are gastrointestinal symptoms. The most serious side effect of deferasirox is potential kidney damage. Up to 30% of patients have transient increases in creatinine that requires temporary modifications of dosing. All patients require monthly chemistry panels and ongoing monitoring for proteinuria. Long-term studies in thousands of patients have not demonstrated progressive renal dysfunction, but isolated cases of renal failure in patients have occurred.

Deferiprone (Ferriprox), an oral iron chelator previously only available in Europe, is approved in the United States. Deferiprone has a half-life of approximately 3 hr and requires 25 mg/kg 3 times a day. Deferiprone, a small molecule, effectively enters cardiac tissue and may be more effective than other chelators in reducing cardiac hemosiderosis. The most serious side effect of deferiprone is transient agranulocytosis, which occurs in 1% of patients. It is associated with rare deaths where patients were not adequately monitored. The use of deferiprone requires weekly white blood cell counts.

As thalassemia patients are living longer, the iron-chelation goals have changed. Aggressive treatment with combination chelation therapy is often used in heavily iron-overloaded patients to prevent or reverse organ dysfunction. Deferoxamine, in combination with deferiprone, is routinely used in patients with increased cardiac iron. Combination therapy of deferoxamine and deferasirox may also be efficacious in similar patients.

Hydroxyurea, a DNA antimetabolite, increases stress erythropoiesis, which results in increased Hbf production. It has been most successfully used in sickle cell disease and in some patients with β-thalassemia intermedia. Studies in β-thalassemia major are limited. In many parts of the world, hydroxyurea therapy is used in thalassemia intermedia patients. Even though increases in Hbf levels are observed, they do not predictively correlate with increase in total hemoglobin in these patients. In general, there appears to be a mean increase in hemoglobin of 1 g (range: 0.1-2.5 g). Hydroxyurea therapy in thalassemia intermedia may have other benefits including decreasing the vascular disease associated with thalassemia intermedia. The initial starting dose for thalassemia intermedia is 10 mg/kg and because these patients are more sensitive to toxicity than sickle cell disease, higher doses are used with great caution.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation has cured >3,000 patients who had β-thalassemia major. In low-risk HLA-matched sibling patients, there is at least a 90% survival and an 80% event-free survival. In general, myeloablative conditioning regimens are required in order to prevent graft rejection and thalassemia recurrence. Most success has been in children younger than 15 yr of age without excessive iron stores and hepatomegaly who undergo sibling HLA-matched allogeneic transplantation. All children who have an HLA-matched sibling should be offered the option of bone marrow transplantation. Alternative transplantation regimens for patients without donors are experimental and have variable success.

Splenectomy

Surgical Asplenia

Splenectomy may be required in thalassemia patients who develop hypersplenism. These patients have a falling steady state hemoglobin and/or a rising transfusion requirement. Overall, splenectomy is less frequently used as a therapeutic option. There is an increased recognition of serious adverse effects of splenectomy beyond infection risk. In thalassemia intermedia, splenectomized patients have a marked increased risk of venous thrombosis, pulmonary hypertension, leg ulcers, and silent cerebral infarction compared to nonsplenectomized patients. All patients should be fully immunized against encapsulated bacteria and should be on long-term penicillin prophylaxis with appropriate instructions regarding fever management. Prophylactic penicillin should be administered postsplenectomy to prevent sepsis, and families need to be educated on the risk of fever and sepsis.

Preventative Monitoring of Thalassemia Patients

Cardiac. Cardiac disease is the major cause of death in thalassemia. Serial echocardiograms should be monitored to evaluate cardiac function and pulmonary artery pressure. Pulmonary hypertension frequently occurs in non-transfused thalassemia patients and may be an indication for transfusion therapy. After 8 yr of chronic transfusion therapy, cardiac hemosiderosis may occur; consequently, cardiac T2* MRI imaging studies are recommended. Patients with cardiac hemosiderosis and decreasing cardiac ejection fraction require intensive combination chelation therapy.

Endocrine. Endocrine function progressively declines with age secondary to hemosiderosis and nutritional deficiencies. Iron deposition in the pituitary and endocrine organs can result in multiple endocrinopathies, including hypothyroidism, growth hormone deficiency, delayed puberty, and hypoparathyroidism, diabetes mellitus, osteoporosis, and adrenal insufficiency. Monitoring for endocrine dysfunction starts early, around 5 yr of age, or after at least 3 yr of chronic transfusions. All children require monitoring of their height, weight, and sitting height semi-annually. Nutritional assessments are required. Most patients need vitamin D, calcium, vitamin B, vitamin C, and zinc replacement. Fertility is a growing concern among patients and should be assessed routinely.

Psychosocial Support. Thalassemia imposes major disruption in the family unit and significant obstacles to normal development. Culturally sensitive anticipatory counseling is necessary, and the early use of child life services decreases psychological trauma of therapy. Early social service consultation to address financial and social issues is mandatory.

OTHER β-THALASSEMA SYNDROMES

Nontransfusion-Dependent Thalassemia: β-Thalassemia Intermedia

The β-thalassemia syndromes are characterized by decreased production of β-globin chains of HbA. There are 200-300 β-thalassemia alleles that have now been characterized. These mutations can affect any step in the transcription of β-globin genes. As discussed, β+/β-thalassemia is absent production of normal β-chains, and production of β− is decreased. Some β-thalassemia mutations have structural mutations such as HbE. Others, such as Hβ-thalassemia or HPFH, are variants of β-thalassemia that have decreased production of β-globin gene with increased compensation of Hbf. Because phenotypic correlation with genotype is variable, β-thalassemia patients are largely classified by their clinical spectrum. Transfusion-dependent thalassemia, or thalassemia major, is the most severe group. Nontransfusion-dependent thalassemia intermedia include a spectrum of patients who initially are not chronically transfused in infancy but may be sporadically transfused throughout their lifetime. The major determining characteristic of these patients is less α-/β-globin chain imbalance than observed in thalassemia major. Sometimes, genetic modifiers alter the primary mutation severity and improve the globin chain imbalance. Coinheritance of α-thalassemia trait or polymorphisms of globin promoters such as BCL11 may convert a thalassemia major patient to a nontransfusion-dependent thalassemia intermedia patient. HbE/β-thalassemia is a common cause of both transfusion-dependent and nontransfusion-dependent thalassemia. These secondary genetic modifiers play a role in altering the severity of this disorder. Occasionally, patients with a single β-thalassemia mutation or autosomal dominant β-thalassemia trait have clinical features of thalassemia intermedia, or nontransfusion-dependent thalassemia. Genetic studies of these patients often uncover a coinheritance of genetic modifiers that worsen the condition such as α-gene triplication or an unstable β-globin mutation.
Thalassemia intermedia patients have significant ineffective erythropoiesis that leads to microcytic anemia with hemoglobin of approximately 7 g/dL (range: 6-10 g/dL). These patients have some of the complications characterized in transfused thalassemia major patients, but the severity varies depending on the degree of ineffective erythropoiesis. They can develop medullary hyperplasia, hepatosplenomegaly, hematopoietic pseudotumors, pulmonary hypertension, thrombotic events, and growth failure. Many patients develop hemosiderosis secondary to increased gastrointestinal absorption of iron requiring chelation. Extramedullary hematopoiesis can occur in the vertebral canal, compressing the spinal cord and causing neurologic symptoms; the latter is a medical emergency requiring immediate local radiation therapy to halt erythropoiesis. Transfusions are indicated in thalassemia intermedia patients with significant clinical morbidity.

Thalassemia trait is often misdiagnosed as iron deficiency in children because the two produce similar hematologic abnormalities on CBC, and iron deficiency is much more prevalent. A short course of iron and reevaluation is all that is required to identify children who will need further evaluation. Children who have β-thalassemia trait have a persistently normal red cell distribution width and low mean corpuscular volume (MCV), whereas patients with iron deficiency develop an elevated red cell distribution width with treatment. On hemoglobin analysis, they have an elevated HbF and usually increased levels of HbA₂. There are “silent” forms of β-thalassemia trait, and if the family history is suggestive, further studies may be indicated.

α-thalassemia syndromes

The same evolutionary pressures that produced β-thalassemia and sickle cell disease produced α-thalassemia. Infants are identified in the newborn period by the increased production of Bart hemoglobin (γ₃) during fetal life and its presence at birth. The α-thalassemia syndromes occur most commonly in Southeast Asia. Deletion mutations are common in α-thalassemia. In addition to deletional mutations, there are nondeletional α-globin gene mutations, the most common being Constant Spring (α⁺α⁰); these mutations cause a more severe anemia and clinical course than the deletional mutations. There are 4 α-globin gene alleles and 4 deletional α-thalassemia phenotypes. The different phenotypes in α-thalassemia largely result from whether one (α⁺/α−) or both (α⁻/α⁻) α-globin genes are deleted in each of the 2 loci.

The deletion of 1 α-globin gene allele (silent trait) is not identifiable hematologically. Specifically, no alterations are noted in the MCV and mean corpuscular hemoglobin. Persons with this deletion are usually diagnosed after the birth of a child with a 2-gene deletion or HbH (HbH trait) or both, but some newborn screening programs report very low concentrations of Hb Bart. During the newborn period, <3% Hb Bart is observed. The deletion of 1 α-globin gene allele is common in African-Americans.

The deletion of 2 α-globin gene alleles results in α-thalassemia trait. The α-globin alleles can be lost in a trans- (α⁺/−α) or cis- (α⁻/α⁻) configuration. The trans or cis mutations can combine with other mutations and lead to HbH or α-thalassemia major. In persons from Africa or of African descent, the most common α-globin deletions are in the trans configuration; whereas, in persons from or descended from Asia or the Mediterranean region, cis deletions are most common.

α-thalassemia trait manifest as a microcytic anemia that can be mistaken for iron-deficiency anemia (see Fig. 462-5F). The hemoglobin analysis is normal, except during the newborn period, when Hb Bart is commonly <8% but >3%. Children with a deletion of 2 α-globin alleles are commonly thought to have iron deficiency, given the presence of both low MCV and mean corpuscular hemoglobin. The simplest approach to distinguish between iron deficiency and α-thalassemia trait is with a good dietary history. Children with iron-deficiency anemia often have a diet that is low in iron and drink significant amount of cow's milk. Alternatively, a brief course of iron supplementation along with monitoring of erythrocyte parameters might confirm the diagnosis of iron deficiency. If both parents of a child diagnosed with α-thalassemia trait are carriers, they are at risk for a future hydrops fetalis pregnancy. Thus, family screening and genetic counseling are indicated.

The deletion of 3 α-globin gene alleles leads to the diagnosis of HbH disease. A more severe form of HbH disease may be caused by a nondeletional α-globin mutation with 2 allele deletions. HbH Constant Spring (α⁺α⁻α⁰) is the most common type of nondeletional HbH disease.

In California, where a large population of persons of Asian descent resides, approximately 1:10,000 of all newborns have HbH disease. The simplest manner of diagnosing HbH disease is during the newborn period, when excess in γ-tetramers are present and Hb Bart is commonly >25%. Obtaining supporting evidence from the parents is also necessary. Later in childhood, there is an excess of β-globin chain tetramers that results in HbH. A definitive diagnosis of HbH disease requires DNA analysis with supporting evidence. Brilliant cresyl blue can stain HbH, but it is rarely used for diagnosis. Patients with HbH disease have a marked microcytosis, anemia, mild splenomegaly, and, occasionally, scleral icterus or cholelithiasis. Chronic transfusion is not commonly required for therapy because the range of hemoglobin is 7-11 g/dL, with MCV 51-73 fl, but intermittent transfusions for worsening anemia may be needed.

The deletion of all 4 α-globin gene alleles causes profound anemia during fetal life, resulting in hydrops fetalis; the ζ-globin gene must be present for fetal survival. There are no normal hemoglobins present at birth (primarily Hb Bart, with Hb Gower 1, Gower 2, and Portland). If the fetus survives, immediate exchange transfusion is indicated. These infants with severe α-thalassemia are transfusion dependent, and hematopoietic stem cell transplantation is the only cure.

Treatment of HbH disease requires ongoing monitoring of growth and organ dysfunction. Dietary supplement with folate and multivitamins without iron is indicated. Older patients may develop decreased bone density with calcium and vitamin D deficiency. Iron supplementation should be avoided. Intermittent transfusion requirements during child development and infection may occur, particularly in nondeleterional HbH. Splenectomy is occasionally indicated and because of the high risk of postsplenectomy thrombosis, aspirin or other anticoagulant therapy following splenectomy should be considered. Hemosiderosis, secondary to gastrointestinal iron absorption and/or transfusion exposure, may develop in older patients and require therapy. Because HbH is an unstable hemoglobin sensitive to oxidative injury, oxidative medications should be avoided. At-risk couples for hydrops fetalis should be identified and offered molecular diagnosis on fetal tissue obtained early in pregnancy. Later in pregnancy, intrauterine transfusion can improve fetal survival, but chronic transfusion therapy or bone marrow transplantation for survivors will be required.

Bibliography is available at Expert Consult.
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Congenital hemolytic anemia occurs in persons homozygous or compound heterozygous for autosomal recessive genes that cause either a marked reduction in red blood cell (RBC) pyruvate kinase (PK) or production of an abnormal enzyme with decreased activity resulting in impaired conversion of phosphoenolpyruvate to pyruvate. Generation of adenosine triphosphate (ATP) within RBCs at this step is impaired, and low levels of ATP, pyruvate, and the oxidized form
of nicotinamide adenine dinucleotide (NAD\(^+\)) are found (Fig. 463-1).
The concentration of 2,3-diphosphoglycerate is increased; this isomer is beneficial in facilitating oxygen release from hemoglobin but detrimental in inhibiting hexokinase and enzymes of the hexose monophosphate shunt. In addition, an unexplained decrease occurs in the sum of the adenine (ATP, adenosine diphosphate; and adenosine monophosphate) and pyridine (NAD\(^+\) and the reduced form of NAD) nucleotides, further impairing glycolysis. As a consequence of decreased ATP, RBCs cannot maintain their potassium and water content; the cells become rigid, and their life span is considerably reduced.

**ETIOLOGY**

There are 2 mammalian PK genes, but only the *PKLR* gene is expressed in red cells. The human *PKLR* gene is located on chromosome 1q21. More than 180 mutations are reported in this structural gene, which codes for a 574-amino-acid protein that forms a functional tetramer. These mutations include missense, splice site, and insertion–deletion alterations, and there is some correlation of the type, location, and amino acid substitution with disease severity. Most affected patients are compound heterozygotes for 2 different PK gene defects. The many possible combinations likely account for the variability in clinical severity. The mutations 1456 C to T and 1529 G to A are the most common mutations in the white population.

**CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS**

The clinical manifestations of PK deficiency vary from severe neonatal hemolytic anemia to mild, well-compensated hemolysis first noted in adulthood. Severe jaundice and anemia may occur in the neonatal period, and kernicterus has been reported. The hemolysis in older children and adults varies in severity, with hemoglobin values ranging from 8-12 g/dL associated with some pallor, jaundice, and splenomegaly. Patients with these findings usually do not require transfusion. A severe form of the disease has a relatively high incidence among the Amish of the midwestern United States. PK deficiency may possibly provide protection against falciparum malaria.

Polychromatophilia and mild macrocytosis reflect the elevated reticulocyte count. Spherocytes are uncommon, but a few spiculated pyknotic cells may be found. Diagnosis relies on demonstration of a marked reduction of RBC PK activity or an increase in the Michaelis–Menten dissociation constant (\(K_m\)) for its substrate, phosphoenolpyruvate (high \(K_m\) variant). Other RBC enzyme activity is normal or elevated, reflecting the reticulocytosis. No abnormalities of hemoglobin are noted. The white cells have normal PK activity and must be rigorously excluded from the red cell hemolysates used to measure PK activity. Heterozygous carriers usually have moderately reduced levels of PK activity.

**TREATMENT**

Phototherapy and exchange transfusions may be indicated for hyperbilirubinemia in newborns. Transfusions of packed RBCs are necessary for severe anemia or for aplastic crises. If the anemia is consistently severe and frequent transfusions are required, iron chelation may be necessary, and splenectomy should be performed after the child is 5-6 yr of age. Although it is not curative, splenectomy may be followed by higher hemoglobin levels and by strikingly high (30-60%) reticulocyte counts. Death resulting from overwhelming pneumococcal sepsis has followed splenectomy; thus, immunization with vaccines for encapsulated organisms should be given before splenectomy, and prophylactic penicillin should be administered after the procedure.
463.2 Other Glycolytic Enzyme Deficiencies

George B. Segel

Chronic nonspherocytic hemolytic anemias of varying severity have been associated with deficiencies of other enzymes in the glycolytic pathway, including hexokinase, glucose phosphate isomerase, and aldolase, which are inherited as autosomal recessive disorders. **Phosphofructokinase deficiency**, which occurs primarily in Ashkenazi Jews in the United States, results in hemolysis associated with a myopathy classified as glycogen storage disease type VII (see Chapter 87.1). Clinically, hemolytic anemia is complicated by muscle weakness, exercise intolerance, cramps, and possibly myoglobinuria. Enzyme assays for phosphofructokinase yield low values for RBCs and muscle.

**Triose phosphate isomerase deficiency** is an autosomal recessive disorder affecting many systems. Affected patients have hemolytic anemia, cardiac abnormalities, and lower motor neuron and pyramidal tract impairment, with or without evidence of cerebral impairment. They usually die in early childhood. The gene for triose phosphate isomerase has been cloned and sequenced and is located on chromosome 12.

**Phosphoglycerate kinase (PGK)** is the first ATP-generating step in glycolysis. At least 23 kindreds with PGK deficiency have been described. PGK is the only glycolytic enzyme inherited on the X chromosome. Affected males may have progressive extrapyramidal disease, myopathy, seizures, and variable mental retardation in conjunction with hemolytic anemia. Nine Japanese patients had neutral or myopathic symptoms with hemolysis; 6 had hemolysis alone; 7 had neutral or myopathic symptoms alone; and 1 had no symptoms. The gene for PGK is particularly large, spanning 23 kb, and various genetic abnormalities, including nucleotide substitutions, gene deletions, missense, and splicing mutations, result in PGK deficiency.

**DEFICIENCIES OF ENZYMES OF THE HEXOSE MONOPHOSPHATE PATHWAY**

The most important function of the hexose monophosphate pathway is to maintain glutathione (GSH) in its reduced state as protection against the oxidation of RBCs (see Fig. 463-1). Approximately 10% of the glucose taken up by RBCs passes through this pathway to provide the reduced form of NADP (NADPH) necessary for the conversion of oxidized GSH to reduced GSH. Maintenance of reduced GSH is essential for the physiologic inactivation of oxidant compounds, such as hydrogen peroxide, that are generated within RBCs. If glutathione, or any compound or enzyme necessary for maintaining it in the reduced state, is decreased, the SH groups of the RBC membrane are oxidized and the hemoglobin becomes denatured and may precipitate into RBC inclusions called **Heinz bodies**. Once Heinz bodies have formed, an acute hemolytic process results from damage to the RBC membrane by the precipitated hemoglobin, the oxidant agent, and the action of the spleen. The damaged RBCs then are rapidly removed from the circulation.

463.3 Glucose-6-Phosphate Dehydrogenase Deficiency and Related Deficiencies

George B. Segel and Lisa R. Hackney

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most frequent disease involving enzymes of the hexose monophosphate pathway, is responsible for 2 clinical syndromes, episodic hemolytic anemia and chronic nonspherocytic hemolytic anemia. The most common manifestations of this disorder are neonatal jaundice and episodic acute hemolytic anemia, which is induced by infections, certain drugs, and, rarely, fava beans. This X-linked deficiency affects more than 400 million people worldwide, representing an overall 4.9% global prevalence. The global distribution of this disorder parallels that of malaria, representing an example of “balanced polymorphism,” in which there is an evolutionary advantage of resistance to falciparum malaria in heterozygous females that outweighs the small negative effect of affected hemizygous males.

The deficiency is caused by inheritance of any of a large number of abnormal alleles of the gene responsible for the synthesis of the G6PD protein. About 140 mutations have been described in the gene responsible for the synthesis of the G6PD protein. Many of these mutations are single base changes leading to amino acid substitutions and destabilization of the G6PD enzyme. A web-accessible database catalogs G6PD mutations (http://www.bioinf.org.uk/g6pd/). Figure 463-2 shows some of the mutations that cause episodic versus chronic hemolysis. Milder disease is associated with mutations near the amino terminus of the G6PD molecule, and chronic nonspherocytic hemolytic anemia is associated with mutations clustered near the carboxyl terminus. The normal enzyme found in most populations is designated G6PD A+. A normal variant, designated G6PD A−, is common in Americans of African descent.

**EPISODIC OR INDUCED HEMOLYTIC ANEMIA**

**Etiology**

G6PD catalyzes the conversion of glucose 6-phosphate to 6-phosphogluconic acid. This reaction produces NADPH, which maintains GSH in the reduced, functional state (see Fig. 463-1). Reduced GSH provides protection against oxidant threats from certain drugs and infections that would otherwise cause precipitation of hemoglobin (Heinz bodies) or damage the RBC membrane.

Synthesis of RBC G6PD is determined by a gene on the X chromosome. Thus, heterozygous females have intermediate enzymatic activity and have 2 populations of RBCs: one is normal, and the other is deficient in G6PD activity. Because they have fewer susceptible cells, most heterozygous females do not have evident clinical hemolysis after exposure to oxidant drugs. Rarely, the majority of RBCs is G6PD deficient in heterozygous females because the inactivation of the normal X chromosome is random and sometimes exaggerated (Lyon-Beutler hypothesis).

Disease involving this enzyme therefore occurs more frequently in males than in females. Approximately 13% of male Americans of African descent have a mutant enzyme (G6PD A−) that results in a deficiency of RBC G6PD activity (5-15% of normal). Italians, Greeks, and other Mediterranean, Middle Eastern, African, and Asian ethnic groups also have a high incidence, ranging from 5% to 40%, of a variant designated G6PD B− (G6PD Mediterranean). In these variants, the G6PD activity of homozygous females or hemizygous males is <5% of normal. Therefore, the defect in Americans of African descent is less severe than that in Americans of European descent. A third mutant enzyme with markedly reduced activity (G6PD Canton) occurs in approximately 5% of the Chinese population.
Clinical Manifestations

Most individuals with G6PD deficiency are asymptomatic, with no clinical manifestations of illness unless triggered by infection, drugs, or ingestion of fava beans. Typically, hemolysis ensues in about 24-48 hr after a patient has ingested a substance with oxidant properties. In severe cases, hemoglobinuria and jaundice result, and the hemoglobin concentration may fall precipitously. Drugs that elicit hemolysis in these individuals include aspirin, sulfonamides, rasburicase, and antimarialars, such as primaquine (Table 463-1). The degree of hemolysis varies with the inciting agent, amount ingested, and severity of the enzyme deficiency. In some individuals, ingestion of fava beans also produces an acute, severe hemolytic syndrome, known as favism. Fava beans contain divicine, isouramil, and convicine, which ultimately lead to production of hydrogen peroxide and other reactive oxygen products. Favism is thought to be more frequently associated with the G6PD B− variant.

In the G6PD A− variant, the stability of the folded protein dimer is impaired, and this defect is accentuated as the RBCs age. Thus, hemolysis decreases as older red cells are destroyed, even if administration of the drug is continued. This recovery results from the age-labile enzyme, which is abundant and more stable in younger RBCs. These young cells have associated reticulocytosis produces a compensated hemolytic process in which the blood hemoglobin may be only slightly decreased, despite continued exposure to the offending agent.

G6PD deficiency can produce hemolysis in the neonatal period. In G6PD A−, spontaneous hemolysis and hyperbilirubinemia have been observed in preterm infants. In newborns with the G6PD B− and G6PD Canton varieties, hyperbilirubinemia and even kernicterus may occur. Neonates with coinheritance of G6PD deficiency and a mutation of the promoter of uridine-diphosphate-glucuronyl transferase (UGT1A1), seen in Gilbert syndrome, have more severe neonatal jaundice. When a pregnant woman ingests oxidant drugs, they may be transmitted to her G6PD-deficient fetus, and hemolytic anemia and jaundice may be apparent at birth.

Laboratory Findings

The onset of acute hemolysis usually results in a precipitous fall in hemoglobin and hematocrit. If the episode is severe, the hemoglobin binding proteins, such as haptoglobin, are saturated, and free hemoglobin may appear in the plasma and subsequently in the urine. Unstained or supravital preparations of RBCs reveal precipitated hemoglobin, known as Heinz bodies. The RBC inclusions are not visible on the Wright-stained blood film. Cells that contain these inclusions are seen only within the first 3-4 days of illness because they are rapidly cleared from the blood. Also, the blood film may contain red cells with what appears to be a bite taken from their periphery and polychromasia (evidence of bluish, larger RBCs), representing reticulocytosis (Fig. 463-3).

Diagnosis

The diagnosis depends on direct or indirect demonstration of reduced G6PD activity in RBCs. By direct measurement, enzyme activity in affected persons is ≤10% of normal, and the reduction of enzyme activity is more extreme in Americans of European descent and in Asians than in Americans of African descent. Satisfactory screening tests are based on decoloration of methylene blue, reduction of methemoglobin, or fluorescence of NADPH. Immediately after a hemolytic episode, reticulocytes and young RBCs predominate. These young cells have significantly higher enzyme activity than do older cells in the A− variant (African). Testing may therefore have to be deferred for a few weeks before a diagnostically low level of enzyme can be shown. The diagnosis can be suspected when G6PD activity is within the low-normal range in the presence of a high reticulocyte count. G6PD variants also can be detected by electrophoretic and molecular analysis. G6PD deficiency should be considered in any neonatal patients with hyperbilirubinemia and borderline low G6PD activity.

Prevention and Treatment

Prevention of hemolysis constitutes the most important therapeutic measure. When possible, males belonging to ethnic groups with a significant incidence of G6PD deficiency (e.g., Greeks, southern Italians, Sephardic Jews, Filipinos, southern Chinese, Americans of African descent, and Thais) should be tested for the defect before known oxidant drugs are given. The usual doses of aspirin and trimethoprim-sulfamethoxazole do not cause clinically relevant hemolysis in the A− variety. Aspirin administered in doses used for acute rheumatic fever (60-100 mg/kg/24 hr) may produce a severe hemolytic episode. Infants with severe neonatal jaundice who belong to these ethnic groups also require testing for G6PD deficiency because of their heightened risk for this defect. If severe hemolysis has occurred,
supportive therapy may require blood transfusions, although recovery is the rule when the oxidant agent is discontinued.

**CHRONIC HEMOLYTIC ANEMIAS ASSOCIATED WITH DEFICIENCY OF G6PD OR RELATED FACTORS**

Chronic nonspherocytic hemolytic anemia has been associated with profound deficiency of G6PD caused by enzyme variants, particularly those defective in quantity, activity, or stability. The gene defects leading to chronic hemolysis are located primarily in the region of the NADP binding site near the carboxyl terminus of the protein (see Fig. 463-2). These include the Loma Linda, Tomah, Iowa, Beverly Hills, Nashville, Riverside, Santiago de Cuba, and Andalus variants. Persons with G6PD B−enzyme deficiency occasionally have chronic hemolysis, and the hemolytic process may worsen after ingestion of oxidant drugs. Splenectomy is of little value in these types of chronic hemolysis.

Other enzyme defects may impair the regeneration of GSH as an oxidant "sump" (see Fig. 463-1). Mild, chronic nonspherocytic anemia has been reported in association with decreased RBC GSH, resulting from γ-glutamylcysteine or GSH synthetase deficiencies. Deficiency of 6-phosphogluconate dehydrogenase has been associated primarily with drug-induced hemolysis, and hemolysis with hyperbilirubinemia has been related to a deficiency of GSH peroxidase in newborn infants.

*Bibliography is available at Expert Consult.*
Bibliography


AUTOIMMUNE HEMOLYTIC ANEMIAS
A number of extrinsic agents and disorders may lead to premature destruction of red blood cells (RBCs). Among the most clearly defined are antibodies associated with immune hemolytic anemias. The hallmark of this group of diseases is the positive result of the direct antiglobulin (Coombs) test, which detects a coating of immunoglobulin or components of complement on the RBC surface. The most important immune hemolytic disorder in pediatric practice is hemolytic disease of the newborn (erythroblastosis fetalis), caused by transplacental transfer of maternal antibody active against the RBCs of the fetus, that is, isoimmune hemolytic anemia (see Chapter 103.2). Various other immune hemolytic anemias are autoimmune (Table 464-1) and may be idiopathic or related to various infections (Epstein-Barr virus, and rarely HIV, cytomegalovirus, and mycoplasma), immunologic diseases (systemic lupus erythematosus [SLE], rheumatoid arthritis), immunodeficiency diseases (agammaglobulinemia, autoimmune lymphoproliferative disorder, dysgammaglobulinemias), neoplasms (lymphoma, leukemia, and Hodgkin disease), or drugs (methyldopa, i-dopa). Other drugs (penicillin, cephalosporins) cause hemolysis by means of "drug-dependent antibodies"—that is, antibodies directed toward the drug and in some cases toward an RBC membrane antigen as well.

### Table 464-1
<table>
<thead>
<tr>
<th>Diseases Characterized by Immune-Mediated Red Blood Cell Destruction</th>
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<tbody>
<tr>
<td><strong>AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY WARM REACTIVE AUTOANTIBODIES</strong></td>
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<td>Primary (idiopathic)</td>
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<td>Immunodeficiency disorders</td>
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<td><strong>AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY COLD REACTIVE AUTOANTIBODIES (CRYOPATHIC HEMOLYTIC SYNDROMES)</strong></td>
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<td>Primary (idiopathic)</td>
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<td>Congenital or tertiary syphilis</td>
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<td><strong>DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA</strong> (see Table 464-2)</td>
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<td>Hapten/drug adsorption (e.g., penicillin)</td>
</tr>
<tr>
<td>Ternary (immune) complex (e.g., quinine or quinidine)</td>
</tr>
<tr>
<td>True autoimmune induction (e.g., methyldopa)</td>
</tr>
</tbody>
</table>


### AUTOIMMUNE HEMOLYTIC ANEMIAS ASSOCIATED WITH “WARM” ANTIBODIES Etiology
In the autoimmune hemolytic anemias, autoantibodies are directed against RBC membrane antigens, but the pathogenesis of antibody induction is uncertain. The autoantibody may be produced as an inappropriate immune response to an RBC antigen or to another antigenic epitope similar to an RBC antigen, known as molecular mimicry. Alternatively, an infectious agent may alter the RBC membrane so that it becomes "foreign" or antigenic to the host. The antibodies usually react to epitopes (antigens) that are “public” or common to all human RBCs, such as Rh proteins.

In most instances of warm antibody hemolysis, no underlying cause can be found; this is the primary or idiopathic type (see Table 464-1). If the autoimmune hemolysis is associated with an underlying disease, such as a lymphoproliferative disorder, SLE, Evans syndrome, or immunodeficiency, it is secondary. In as many as 20% of cases of immune hemolysis, drugs may be implicated (Table 464-2).

Drugs (penicillin or sometimes cephalosporins) that cause hemolysis via the “hapten” mechanism (immune but not autoimmune) bind tightly to the RBC membrane (see Table 464-1). Antibodies to the drug, either newly or previously formed, bind to the drug molecules on RBCs, mediating their destruction in the spleen. In other cases, certain drugs, such as quinine and quinidine, do not bind to RBCs but, rather, form part of a “ternary complex,” consisting of the drug, an RBC membrane antigen, and an antibody that recognizes both (see Table 464-1). Methyldopa and sometimes cephalosporins may, by unknown mechanisms, incite true autoantibodies to RBC membrane antigens, so that the presence of the drug is not required to cause hemolysis. Cephalosporins are the most common cause of drug-immune hemolytic anemia.

### Clinical Manifestations
Autoimmune hemolytic anemias may occur in either of 2 general clinical patterns. The first, an acute transient type lasting 3-6 mo and occurring predominantly in children ages 2-12 yr, accounts for 70-80% of patients. It is frequently preceded by an infection, usually respiratory.
Onset may be acute, with prostration, pallor, jaundice, fever, and hemoglobinuria, or more gradual, with primarily fatigue and pallor. The spleen is usually enlarged and is the primary site of destruction of immunoglobulin (Ig) G–coated RBCs. Underlying systemic disorders are unusual. A consistent response to glucocorticoid therapy, a low mortality rate, and full recovery are characteristic of the acute form. The other clinical pattern involves a prolonged and chronic course, which is more frequent in infants and in children >12 yr old. Hemolysis may continue for many months or years. Abnormalities involving other blood elements are common, and the response to glucocorticoids is variable and inconsistent. The mortality rate is approximately 10%, and death is often attributable to an underlying systemic disease.

**Laboratory Findings**

In many cases, anemia is profound, with hemoglobin levels <6 g/dL. Considerable spherocytosis and polychromasia (reflecting the reticulocyte response) are present. More than 50% of the circulating RBCs may be reticulocytes, and nucleated RBCs usually are present. In some cases, a low reticulocyte count may be found, particularly early in the episode. Leukocytosis is common. The platelet count is usually normal, but concomitant immune thrombocytopenic purpura sometimes occurs (Evans syndrome). The prognosis for patients with Evans syndrome is guarded, because many have or eventually have a chronic disease, including SLE, an immunodeficiency syndrome, or the autoimmune lymphoproliferative syndrome.

Results of the direct antiglobulin test are strongly positive, and free antibody can sometimes be demonstrated in the serum (indirect Coombs test). These antibodies are active at 35-40°C (95-104°F) ("warm" antibodies) and most often belong to the IgG class. They do not require complement for activity and are usually incomplete antibodies that do not produce agglutination in vitro. Antibodies from the serum and those eluted from the RBCs react with the RBCs of many persons in addition to those of the patient. They often have been regarded as nonspecific panagglutinins, but careful studies have revealed specificity for RBC antigens of the Rh system in 70% of patients (>50% of adult patients). Complement, particularly fragments of C3b, may be detected on the RBCs in conjunction with IgG. The Coombs test result is rarely negative because of the limited sensitivity of the Coombs reaction. A minimum of 260-400 molecules of IgG per cell is necessary on the RBC membrane to produce a positive reaction. Special tests are required to detect the antibody in cases of "Coombs-negative" autoimmune hemolytic anemia. In warm antibody hemolytic anemia, the direct Coombs test may detect IgG alone, both IgG– and complement fragments, or solely complement fragments if the level of RBC-bound IgG is below the detection limit of the anti-IgG Coombs reagent.

**Treatment**

Transfusions may provide only transient benefit but may be lifesaving in cases of severe anemia by providing delivery of oxygen until the effect of other treatment is observed. All tested units for transfusion are serologically incompatible. It is important to identify the patient’s ABO blood group to avoid a hemolytic transfusion reaction mediated by anti-A or anti-B. The blood bank should also test for the presence of an underlying alloantibody, which could cause rapid hemolysis of transfused red cells. Patients who have neither been previously transfused nor pregnant are unlikely to harbor an alloantibody. Early consultation between the clinician and the blood bank physician is essential. Failure to transfuse a profoundly anemic infant or child may lead to serious morbidity and even death.

Patients with mild disease and compensated hemolysis may not require any treatment. If the hemolysis is severe and results in significant anemia or symptoms, treatment with glucocorticoids is initiated. Glucocorticoids decrease the rate of hemolysis by blocking macrophage function by downregulating Fcγ receptor expression, decreasing the production of the autoantibody, and perhaps enhancing the elution of antibody from the RBCs. Prednisone or its equivalent is administered at a dose of 2 mg/kg/24 hr. In some patients with severe hemolysis, doses of prednisone of up to 6 mg/kg/24 hr may be required to reduce the rate of hemolysis. Treatment should be continued until the rate of hemolysis decreases, and then the dose gradually reduced. If relapse occurs, resumption of the full dosage may be necessary. The disease tends to remit spontaneously within a few weeks or months. The Coombs test result may remain positive even after the hemoglobin level returns to normal. It is usually safe to discontinue prednisone once the direct Coombs test result becomes negative. When hemolytic anemia remains severe despite glucocorticoid therapy, or if very large doses are necessary to maintain a reasonable hemoglobin level, IV immunoglobulin may be tried. Rituximab, a monoclonal antibody that targets B lymphocytes, the source of antibody production, is useful in chronic cases refractory to conventional therapy. Plasmapheresis has been used in refractory cases but generally is not helpful. Splenectomy may be beneficial but is complicated by a heightened risk of infection with encapsulated organisms, particularly in patients <6 yr. Prophylaxis with appropriate vaccines (pneumococcal, meningococcal, and Haemophilus influenzae type b) before splenectomy and with oral penicillin after splenectomy are indicated.

**Course and Prognosis**

Acute idiopathic autoimmune hemolytic disease in childhood varies in severity but is self-limited; death from untreated anemia is rare. Approximately 30% of patients have chronic hemolysis, often associated with an underlying disease, such as SLE, lymphoma, or leukemia.
The presence of antiphospholipid antibodies in adult patients with immune hemolysis predisposes to thrombosis. Mortality in chronic cases depends on the primary disorder.

**AUTOIMMUNE HEMOLYTIC ANEMIAS ASSOCIATED WITH “COLD” ANTIBODIES**

“Cold” antibodies agglutinate RBCs at temperatures <37°C (98.6°F). They are primarily of the IgM class and require complement for hemolytic activity. The highest temperature at which RBC agglutination occurs is called the thermal amplitude. A higher thermal amplitude antibody—that is, one that can bind to RBCs at temperatures achievable in the body—results in hemolysis with exposure to a cold environment. High antibody titers are associated with a high thermal amplitude.

**Cold Agglutinin Disease**

Cold antibodies usually have specificity for the oligosaccharide antigens of the I/i system. They may occur in primary or idiopathic cold agglutinin disease, secondary to infections such as those from *Mycoplasma pneumoniae* and Epstein-Barr virus, or secondary to lymphoproliferative disorders. After *M. pneumoniae* infection, the anti-I levels may increase considerably, and occasionally, enormous increases may occur to titers ≥1/30,000. The antibody has specificity for the I antigen and thus reacts poorly with human cord RBCs, which possess the i antigen but exhibit low levels of I. Patients with infectious mononucleosis occasionally have cold agglutinin disease, and the antibodies in these patients often have anti-i specificity. This antibody causes less hemolysis in adults than in children because adults have fewer i molecules on their RBCs. Spontaneous RBC agglutination is observed in the cold and in vitro, and RBC aggregates are seen on the blood film. Mean corpuscular volume may be spuriously elevated because of RBC agglutination. The severity of the hemolysis is related to the thermal amplitude of the antibody, which itself partly depends on the IgM antibody titer.

When very high titers of cold antibodies are present and active near body temperature, severe intravascular hemolysis with hemoglobinemia and hemoglobinuria may occur and may be heightened on a patient’s exposure to cold (external temperature or ingested foods). Each IgM molecule has the potential to activate a C1 molecule so that large amounts of complement are found on the RBCs in cold agglutinin disease. These sensitized RBCs may undergo intravascular complement-mediated lysis or may be destroyed in the liver and spleen. Only complement, not IgM, is detected on RBCs because the IgM is removed during the washing steps of the direct antiglobulin test.

Cold agglutinin disease is less common in children than in adults and more frequently results in an acute, self-limited episode of hemolysis. Glucocorticoids are much less effective in cold agglutinin disease than in disease with warm antibodies. Patients should avoid exposure to cold and should be treated for underlying disease. In the uncommon patients with severe hemolytic disease, treatment includes immunosuppression and plasmapheresis. Successful treatment of cold agglutinin disease has been reported with the monoclonal antibody rituximab, which effectively depletes B lymphocytes. Splenectomy is not useful in cold agglutinin disease.

**Paroxysmal Cold Hemoglobinuria**

Paroxysmal cold hemoglobinuria is mediated by the Donath-Landsteiner (D-L) hemolysin, which is an IgG cold-reactive autoantibody with anti-P specificity. In vitro, the D-L antibody binds to RBCs in the cold and the RBCs are lysed by complement as the temperature is increased to 37 degrees C. A similar sequence is thought to occur in vivo as RBCs move from the cooler extremities to warmer parts of the circulation. Most reported cases are self-limited; many patients experience only one paroxysm of hemolysis. Congenital or acquired syphilis used to be the most common underlying cause of paroxysmal cold hemoglobinuria, but today, most cases are associated with nonspecific viral infections. This disorder accounts for 30% of immune hemolytic episodes among children. Treatment includes transfusion for severe anemia and avoidance of cold ambient temperatures.

*Bibliography is available at Expert Consult.*
Bibliography


Chapter 465
Hemolytic Anemias Secondary to Other Extracellular Factors
George B. Segel

FRAGMENTATION HEMOLYSIS
(See Table 457-1 in Chapter 457.)
Red blood cell (RBC) destruction may occur in hemolytic anemias because of mechanical injury as the cells traverse a damaged vascular bed. Damage may be microvascular when RBCs are sheared by fibrin in the capillaries during intravascular coagulation or when renovascular disease accompanies the hemolytic-uremic syndrome (HUS) (see Chapter 518) or thrombotic thrombocytopenic purpura (see Chapter 484.5). Larger vessels may be involved in Kasabach-Merritt syndrome (giant hemangiomia and thrombocytopenia; see Chapter 505) or when a replacement heart valve is poorly epithelialized. The blood film shows many “schistocytes,” or fragmented cells, as well as polychromatophilia, reflecting the reticulocytosis (see Fig. 458-4 in Chapter 458). Secondary iron deficiency may complicate the intravascular hemolysis because of urinary hemoglobin and hemosiderin iron loss (see Fig. 457-2 in Chapter 457). Treatment should be directed toward the underlying condition, and the prognosis depends on the effectiveness of this treatment. The benefit of transfusion may be transient because the transfused cells are destroyed as quickly as those produced by the patient.

It is critical to determine the precise etiology of the fragmentation hemolysis because the treatment depends on the underlying problem (Table 465-1). Thrombotic thrombocytopenic purpura results from an antibody to an enzyme (AdamTS13) that regulates the size of von Willebrand multimers. The lack of this enzyme results in a marked increase in multimer size and a resultant thrombotic microangiopathy. The treatment involves plasmapheresis (PLEX) to remove the antibody and replace the AdamTS13. In contrast, HUS results from Shiga toxin produced by Escherichia coli 0157 and may not be helped by PLEX. Atypical HUS involves activation of the alternative complement pathway and is currently treated with eculizumab (anti C5), an inhibitor of the complement pathway. PLEX may reduce the RBC fragmentation and improve the platelet count but has little effect on the tissue (kidney) vasculopathy and thus is not usually recommended. Pneumococcal-induced HUS results from neuraminidase produced by the bacteria, which damages the membranes of the RBCs and the kidney, exposing the T-antigen. Plasma contains natural antibody to the T-antigen producing hemolysis, renal damage, and a thrombotic microangiopathy.

THERMAL INJURY
Extensive burns may directly damage the RBCs and cause hemolysis that results in the formation of spherocytes. Blood loss and marrow suppression may contribute to anemia and require blood transfusion. Erythropoietin (EPO) has been used as treatment for diminished RBC production.

RENAL DISEASE
The anemia of uremia is multifactorial in origin. EPO production may be decreased and the marrow suppressed by toxic metabolites. Furthermore, the RBC life span often is shortened owing to retention of
metabolites and organic acidemia. The use of EPO in chronic renal disease has markedly decreased the need for blood transfusion.

**LIVER DISEASE**
A change in the ratio of cholesterol to phospholipids in the plasma may result in changes in the composition of the RBC membrane and shortening of the RBC life span. Some patients with liver disease have many target RBCs on the blood film, whereas others have a preponderance of spiculated cells. These morphologic changes reflect the alterations in the plasma lipid composition.

**TOXINS AND VENOMS**
Bacterial sepsis caused by Haemophilus influenzae, staphylococci, or streptococci may be complicated by accompanying hemolysis. Particularly severe hemolytic anemia has been observed in clostridial infections and results from a hemolytic clostridial toxin. Large numbers of spherocytes may be seen on the blood film. Spherocytic hemolysis also may be noted after bites by various snakes, including cobras, vipers, and rattlesnakes, which have phospholipases in their venom. Large numbers of bites by insects, such as bees, wasps, and yellow jackets, also may cause spherocytic hemolysis by a similar mechanism (see Chapter 725).

**WILSON DISEASE**
(See Chapter 357.2.)
An acute and self-limited episode of hemolytic anemia may precede by years the onset of hepatic or neurologic symptoms in Wilson disease. This event appears to result from the toxic effects of free copper on the RBC membrane. The blood film often (but not always) shows large numbers of spherocytes, and the Coombs test result is negative. Because early diagnosis of Wilson disease permits prophylactic treatment with penicillamine and prevention of hepatic and neurologic disease, correct assessment of this rare type of hemolysis is important.

*Bibliography is available at Expert Consult.*

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**Table 465-1**

<table>
<thead>
<tr>
<th>DISEASE*</th>
<th>PATHOPHYSIOLOGY</th>
<th>LAB FINDINGS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP</td>
<td>Ab to AdamTS13</td>
<td>AdamTS13 &lt;10%†</td>
<td>PLEX with plasma</td>
</tr>
<tr>
<td>HUS</td>
<td>E. coli 0157, Shiga toxin</td>
<td>E. coli 0157, Shiga toxin</td>
<td>Supportive ? value of PLEX</td>
</tr>
<tr>
<td>aHUS</td>
<td>Complement-mediated alternative pathway</td>
<td>AdamTS13 &gt;10% Decreased factors H and I (inhibitors of complement)‡</td>
<td>Eculizumab (ab to C5) PLEX not indicated</td>
</tr>
<tr>
<td>Pneumococcal-induced HUS</td>
<td>Neuraminidase-induced RBC, platelet, and kidney damage Exposure of T-antigen on RBC and kidney</td>
<td>Pneumococcal infection AdamTS13 &gt;10%</td>
<td>PLEX with albumin for neuraminidase and endogenous T ab removal</td>
</tr>
<tr>
<td>DIC</td>
<td>Sepsis, shock, endotoxin</td>
<td>Decreased fibrinogen, increased fibrin split products, decreased clotting factors and platelets</td>
<td>Treat underlying condition; replace factors and platelets if bleeding</td>
</tr>
</tbody>
</table>

*All show fragmentation hemolytic anemia, thrombocytopenia and potential renal and other organ damage. An elevated lactate dehydrogenase and reduced haptoglobin usually are present secondary to hemolysis.
†Rarely a congenital defect in AdamTS13.
‡May be related to inherited defect in factor H or I.
Ab/ab, antibody; aHUS, atypical hemolytic uremic syndrome; DIC, disseminated intravascular coagulation; E. coli, Escherichia coli; HUS, hemolytic uremic syndrome; PLEX, plasmapheresis; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.
Bibliography
Section 4
Polycythemia (Erythrocytosis)

Chapter 466
Polycythemia
Amanda M. Brandow and Bruce M. Camitta

Polycythemia exists when the red blood cell (RBC) count, hemoglobin level, and total RBC volume all exceed the upper limits of normal. In postpubertal individuals, an RBC mass >25% above the mean normal value (based on body surface area) or a hemoglobin >18.5 g/dL (in males) or >16.5 g/dL (in females) indicate absolute erythrocytosis. A decrease in plasma volume, such as occurs in acute dehydration and burns, may result in a high hemoglobin value. These situations are more accurately designated as hemoconcentration or relative polycythemia because the RBC mass is not increased and normalization of the plasma volume restores hemoglobin to normal levels. Once the diagnosis of true polycythemia is made, sequential studies should be done to determine the underlying etiology (Fig. 466-1).

CLONAL (PRIMARY) POLYCYTHEMIA (POLYCYTHEMIA RUBRA VERA)
Pathogenesis
Polycythemia vera is an acquired clonal myeloproliferative disorder. Although primarily manifesting as erythrocytosis, thrombocytosis and leukocytosis can also be seen. When isolated severe thrombocytosis exists in the absence of erythrocytosis, the myeloproliferative disorder is called essential thrombocytopenia. Polycythemia vera is rare in children. A gain-of-function mutation of JAK2, a cytoplasmic tyrosine kinase, is found in more than 90% of adult patients with polycythemia vera, but in <30% of children with this condition. The erythropoietin
Table 466-1  WHO Diagnostic Criteria for Polycythemia Vera

**MAJOR CRITERIA**
1. Hb >18.5 g/dL (men) or Hb >16.5 g/dL (women) or Hb or Hct >99th percentile of reference range for age, sex, or altitude of residence or Hb >17 g/dL (men) or Hb >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency or elevated red cell mass >25% above mean normal predicted value
2. Presence of JAK2 or similar mutation

**MINOR CRITERIA**
1. Bone marrow trilineage myeloproliferation
2. Subnormal serum erythropoietin level
3. Endogenous erythroid colony growth

**DIAGNOSIS**
Both major criteria and one minor criteria or first major criteria and 2 minor criteria.

Hb, hemoglobin; Hct, hematocrit.


**Figure 466-1** Sequential studies to evaluate polycythemia. CBC, complete blood count; CNS, central nervous system; COHgb, carboxyhemoglobin; 2,3-DPG, 2,3-diphosphoglycerate.

**Clinical Manifestations**

Patients with polycythemia vera usually have hepatosplenomegaly. Erythrocytosis may cause hypertension, headache, shortness of breath, or neurologic symptoms and increases the risk of thrombosis. Granulocytosis may cause diarrhea or pruritus from histamine release. Thrombocytosis (with or without platelet dysfunction) may cause thrombosis or hemorrhage. Table 466-1 lists the diagnostic criteria for polycythemia vera.

**Treatment**

Phlebotomy is the initial treatment of choice to alleviate symptoms of hyperviscosity and decrease the risk of thrombosis. Iron supplementation should be given to prevent viscosity problems from iron-deficient microcytosis or thrombocytosis. In patients with marked thrombocytosis, antiplatelet agents (e.g., aspirin) may reduce the risks of thrombosis and bleeding. If these treatments are unsuccessful or the patient has progressive hepatosplenomegaly, antiproliferative treatments (hydroxyurea, anagrelide, interferon-α) may be helpful. The use of JAK2 inhibitors is an active area of investigation. Transformation of the disease into myelofibrosis or acute leukemia is rare in children. Prolonged survival is not unusual.

*Bibliography is available at Expert Consult.*
Bibliography


Chapter 467
Non-Clonal Polycythemia
Amanda M. Brandow and Bruce M. Camitta

PATHOGENESIS
Nonclonal polycythemia is diagnosed when polycythemia is caused by a physiologic process that is not derived from a single cell (Table 467-1). Nonclonal polycythemia can be congenital or acquired (secondary).

Congenital Polycythemia
Lifelong or familial polycythemia should trigger a search for a congenital problem. These inherited conditions may be transmitted as dominant or recessive disorders. Autosomal dominant causes include hemoglobins that have increased oxygen affinity ($P_{50}$ [partial pressure of oxygen in the blood at which the hemoglobin is 50% saturated] <20 mm Hg), erythropoietin receptor mutations resulting in an enhanced effect of erythropoietin or mutations in the von Hippel–Lindau gene that result in altered intracellular oxygen sensing. Another rare cause is autosomal recessive 2,3-diphosphoglyceric acid deficiency, which leads to a left shift of the oxygen dissociation curve, increased oxygen affinity, and consequent polycythemia.
**Table 467-1 Differential Diagnosis of Polycythemia**

<table>
<thead>
<tr>
<th>Type</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLONAL (PRIMARY)</td>
<td>Polycythemia vera</td>
</tr>
</tbody>
</table>
| NONCLONAL          | **Congenital** High-oxygen affinity hemoglobinopathy (e.g., hemoglobin Chesapeake, Malmo, San Diego)  
                      | Erythropoietin receptor mutations (primary familial and congenital polycythemia [PFCP])  
                      | Methemoglobin reductase deficiency  
                      | Hemoglobin M disease  
                      | 2,3-Diphosphoglycerate deficiency |
| Acquired           | Hormonal  
                      | Adrenal disease  
                      | Virilizing hyperplasia, Cushing syndrome  
                      | Anabolic steroid therapy  
                      | Malignant tumors  
                      | Adrenal, cerebellar, hepatic, other  
                      | Renal disease  
                      | Cysts, hydronephrosis, renal artery stenosis  
                      | Hypoxia  
                      | Altitude  
                      | Cardiac disease  
                      | Lung disease  
                      | Central hypoventilation  
                      | Chronic carbon monoxide exposure  
                      | Neonatal  
                      | Delayed cord clamping (placental-fetal transfusion)  
                      | Normal intrauterine environment  
                      | Placental insufficiency (preeclampsia, maternal chronic hypertension, placental abruption)  
                      | Twin–twin or maternal–fetal hemorrhage  
                      | Perinatal asphyxia  
                      | Infants of diabetic mothers  
                      | Intrauterine growth retardation  
                      | Trisomy 13, 18, or 21  
                      | Adrenal hyperplasia  
                      | Thyrotoxicosis  
                      | Spurious  
                      | Plasma volume decrease |

Subtle decreases in oxygen delivery to tissues may cause polycythemia. Congenital methemoglobinemia resulting from an autosomal recessive deficiency of cytochrome b5 reductase may cause cyanosis and polycythemia (see Chapter 462.7). Most affected individuals are asymptomatic. Neurologic abnormalities may be present in patients whose enzyme deficits are not limited to hematopoietic cells. Hemoglobin M disease (autosomal dominant) causes methemoglobinemia and can lead to polycythemia. Cyanosis may occur in the presence of as little as 1.5 g/dL of methemoglobin but is uncommon in other hemoglobin variants unless hyperviscosity results in localized hypoxemia.

**Acquired Polycythemia**

Polycythemia may be present in clinical situations associated with chronic arterial oxygen desaturation. Cardiovascular defects involving right-to-left shunts and pulmonary diseases interfering with proper oxygenation are the most common causes of hypoxic polycythemia. Clinical findings usually include cyanosis, hyperemia of the sclerae and mucous membranes, and clubbing of the fingers. As the hematocrit rises to >65%, clinical manifestations of hyperviscosity, such as headache and hypertension, may require phlebotomy. Living at high altitudes also causes hypoxic polycythemia; the hemoglobin level increases approximately 4% for each rise of 1,000 m in altitude. Partial obstruction of a renal artery rarely results in polycythemia. Polycythemia has also been associated with benign and malignant tumors that secrete erythropoietin. Exogenous or endogenous excess of anabolic steroids also may cause polycythemia. A common spurious cause is a decrease in plasma volume such as in moderate to severe dehydration.

**DIAGNOSIS**

Figure 466-1 outlines sequential studies to evaluate polycythemia.

**TREATMENT**

For mild disease, observation is sufficient. When the hematocrit is >65-70% (hemoglobin >23 g/dL), blood viscosity markedly increases. Periodic phlebotomy may prevent or decrease symptoms such as headache, dizziness, or exertional dyspnea. Apheresed blood should be replaced with plasma or saline to prevent hypovolemia in patients accustomed to a chronically elevated total blood volume. Increased demand for red blood cell production may cause iron deficiency. Iron-deficient microcytic red cells are more rigid, further increasing the risk of intracranial and other thromboses in patients with polycythemia. Periodic assessment of iron status, with treatment of iron deficiency, should be performed.

Bibliography is available at Expert Consult.
Bibliography


Pancytopenia refers to a reduction below normal values of all 3 peripheral blood lineages: leukocytes, platelets, and erythrocytes. Pancytopenia requires microscopic examination of a bone marrow biopsy specimen and a marrow aspirate to assess overall cellularity and morphology. There are 3 general categories of pancytopenia depending on the marrow findings.

Hypocellular marrow on biopsy is seen with inherited (“constitutional”) marrow failure syndromes, acquired aplastic anemia of varied etiologies (see Chapter 469), the hypoplastic variant of myelodysplastic syndrome (MDS), and some cases of paroxysmal nocturnal hemoglobinuria with pancytopenia.

Cellular marrow is seen (a) with primary bone marrow disease, such as acute leukemia (see Chapter 494), and MDS, and (b) secondary to systemic disease, such as autoimmune disorders (systemic lupus erythematosus; Chapter 158), vitamin B₁₂ or folate deficiency (see Chapters 49.6 and 49.7), storage disease (Gaucher and Niemann-Pick diseases; see Chapter 86.4), overwhelming infection, sarcoidosis, and hypersplenism.

Bone marrow infiltration can cause pancytopenia in metastatic solid tumors, myelofibrosis, hemophagocytic lymphohistiocytosis (see Chapter 507) and osteopetrosis (see Chapter 699).

Inherited (“constitutional”) pancytopenia is defined as a decrease in marrow production of the 3 major hematopoietic lineages that occurs on an inherited basis, resulting in anemia, neutropenia, and thrombocytopenia. Any of these conditions (Tables 468-1 and 468-2) can be transmitted as a simple mendelian disorder by mutant genes with inherited patterns of autosomal dominant, autosomal recessive, or X-linked types. Modifying genes and acquired factors may also be operative. Inherited pancytopenias account for approximately 30% of cases of pediatric marrow failure. Fanconi anemia is the most common of these disorders.
FANCONI ANEMIA

Etiology and Epidemiology

Fanconi anemia (FA) is primarily inherited in an autosomal recessive manner (one uncommon form is X-linked recessive). It occurs in all racial and ethnic groups. At presentation, patients with FA may have: (1) typical physical anomalies and abnormal hematologic findings (majority of the patients); (2) normal physical features but abnormal hematologic findings (about one-third of patients); or (3) physical anomalies and normal hematologic findings (unknown percentage). There can be sibling discordance in clinical and hematologic findings, even in affected monozygotic twins. Approximately 75% of patients are 3-14 yr of age at the time of diagnosis.

Pathology

Patients have abnormal chromosome fragility, which is seen in metaphase preparations of peripheral blood lymphocytes cultured with phytohemagglutinin and enhanced by adding clastogenic agents such as diepoxybutane (DEB) and mitomycin C. Cell fusion of FA cells with normal cells or with cells from some unrelated patients with FA produces a corrective effect on chromosomal fragility, a process called complementation. This phenomenon allows subtyping of cases of FA into discrete complementation groups. Fifteen different complementation groups have been identified with different FA (FANC) genes that are mutated in each of them: A, B, C, D1/BRCA2, D2, E, F, G, I, J, L, M, N, O, P). An additional 2 genes, XRC2 and ECCR4, have been published and need further studies. After their discovery, the genes are prefixed with FANC (FANC, FANCB, and so on). FANC D1 is identical to the breast cancer susceptibility gene, BRCA2. The protein products of wild-type FANC genes are involved in the DNA damage recognition and repair biochemical pathways. Therefore, mutant gene proteins lead to genomic instability and chromosome fragility. An inability of FA cells to remove oxygen-free radicals, resulting in oxidative damage, is an additional mechanism that may contribute to the disease pathogenesis. Leukocyte telomere length is significantly shortened but telomerase activity is increased, suggesting a high proliferative rate of marrow progenitors that ultimately leads to their premature senescence. Increased marrow cell apoptosis occurs and is

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Table 468-1

Inherited Pancytopenia Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td>Congenital amegakaryocytic thrombocytopenia</td>
</tr>
<tr>
<td>Unclassified inherited bone marrow failure syndromes</td>
</tr>
<tr>
<td>Other genetic syndromes</td>
</tr>
<tr>
<td>Down syndrome</td>
</tr>
<tr>
<td>Dubowitz syndrome</td>
</tr>
<tr>
<td>Seckel syndrome</td>
</tr>
<tr>
<td>Schimke immunooosseous dysplasia</td>
</tr>
<tr>
<td>Cartilage-hair hypoplasia</td>
</tr>
<tr>
<td>Noonan syndrome</td>
</tr>
</tbody>
</table>

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Table 468-2

Distinguishing Clinical Features of the Inherited Bone Marrow Failure Syndromes That May Be Initially Diagnosed in Adulthood

<table>
<thead>
<tr>
<th>DISEASES</th>
<th>Fanconi Anemia</th>
<th>Dyskeratosis Congenita</th>
<th>Schwachman-Diamond Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>Skeletal and renal malformations, low birthweight, pancytopenia, family member with bone marrow failure, MDS, acute myelogenous leukemia (AML), or squamous cell carcinoma at an early age; family member with Fanconi anemia</td>
<td>Intrauterine growth retardation, developmental delay, and short stature. Family history of MDS, AML, marrow failure, abnormal fingernails or toenails, leukoplakia, head and neck cancer, or pulmonary fibrosis</td>
<td>Pancreatic insufficiency, low birth weight, metaphyseal dysostosis, initial neutropenia, delayed development</td>
</tr>
<tr>
<td><strong>Physical findings</strong></td>
<td>Thumb and radial malformations, hyperpigmented skin lesions (café-au-lait spots), short stature, MDS, AML, squamous cell carcinoma at young age, renal and cardiac malformations, microcephaly, hypogonadism</td>
<td>Lacy reticular pigmentation of skin, dystrophic fingernails and toenails, premature graying of hair, hair loss, short stature, oral leukoplakia, squamous cell cancer of head and neck, pulmonary fibrosis, osteopenia, hypogonadism</td>
<td>Short stature, abnormal thorax</td>
</tr>
<tr>
<td><strong>Genes inactivated</strong></td>
<td>FANCA, FANCB, FANCC, FANCD1 (aka BRCA2), FANCD2, FA NCE, FANCF, FANCG (aka XRCC9), FANCI, FANCJ (aka BACH1 and BRIP1), FANCL (aka PHP9 and POG), FANCM (aka He), and FANCN (aka PALB2) These genes encode proteins known to protect the genome from excessive damage induced by chemical crosslinking agents. These genes account for most cases of Fanconi anemia</td>
<td>DKC1, TERC, TERT, TINF2, NOL2, and NOLA3 These genes encode proteins known to participate in maintenance of telomeres. They account for only half of dyskeratosis cases, so there are additional genes to be discovered</td>
<td>SBDS autosomal recessive marrow clonal expansion in –15%</td>
</tr>
<tr>
<td><strong>Screening and diagnostic tests</strong></td>
<td>1. Chromosomal breakage test (in response to mitomycin C or diepoxybutane) 2. Complementation analysis (flow cytometric analysis of G2 arrest in melphalan-exposed cells after transduction with retroviral vectors expressing normal Fanconi anemia genes) 3. Gene sequencing</td>
<td>1. Quantitative analysis of telomere length (“flow FISH”) 2. Gene sequencing</td>
<td>CT demonstrates fatty infiltration of pancreas Gene testing May evolve to myelodysplasia or leukemia Absence of pancreatic lipomatosis, fecal fat, or dysostosis does not rule out diagnosis</td>
</tr>
</tbody>
</table>

ADA, adenosine deaminase; FISH, fluorescent in situ hybridization.

mediated by Fas, a membrane glycoprotein receptor containing an integral death domain. A consistent finding is diminished cellular interleukin-6 production along with markedly heightened tumor necrosis factor-α generation.

**Clinical Manifestations**

The most common anomaly in FA is hyperpigmentation of the trunk, neck, and intertriginous areas, as well as café-au-lait spots and vitiligo, alone or in combination (Fig. 468-1 and Table 468-3). Half the patients have short stature. In some patients, growth failure is aggravated by abnormal growth hormone secretion or with hypothyroidism. Absence of radii and thumbs that are hypoplastic, supernumerary, bifid, or absent are common. The “r” radial pulse may be weak or absent. Anomalies of the feet, congenital hip dislocation, and leg abnormalities are seen. A male patient with FA may have an underdeveloped penis; undescended, atrophic, or absence of the testes; and hypospadias or phimosis. Females can have malformations of the vagina, uterus, and ovary. Many patients have a FA “facies,” including microcephaly, small eyes, epicanthal folds, and abnormal shape, size, or positioning of the ears (Fig. 468-1). Ectopic, pelvic, or horseshoe kidneys are detected by imaging and may show other organs as duplicated, hypoplastic, dysplastic, or absent kidneys. Cardiovascular and gastrointestinal malformations also occur. Approximately 10% of patients with FA are cognitively delayed.

**Table 468-3**  Characteristic Physical Anomalies in Fanconi Anemia

<table>
<thead>
<tr>
<th>ANOMALY</th>
<th>APPROXIMATE FREQUENCY (% OF PATIENTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin pigment changes ± café-au-lait spots</td>
<td>55</td>
</tr>
<tr>
<td>Short stature</td>
<td>51</td>
</tr>
<tr>
<td>Upper limb abnormalities (thumbs, hands, radii, ulnas)</td>
<td>43</td>
</tr>
<tr>
<td>Hypogonadal and genital changes (mostly male)</td>
<td>35</td>
</tr>
<tr>
<td>Other skeletal findings (head/face, neck, spine)</td>
<td>30</td>
</tr>
<tr>
<td>Eye/lid/epicanthal fold anomalies</td>
<td>23</td>
</tr>
<tr>
<td>Renal malformations</td>
<td>21</td>
</tr>
<tr>
<td>Gastrointestinal/cardiovascular malformations</td>
<td>11</td>
</tr>
<tr>
<td>Hip, leg, foot, toe abnormalities</td>
<td>10</td>
</tr>
<tr>
<td>Ear anomalies (external and internal), deafness</td>
<td>9</td>
</tr>
</tbody>
</table>

Figure 468-1  A 3 yr old boy with Fanconi anemia who exhibits several classic phenotype features. A, Front view. B, Face. C, Hands. D, Back right shoulder. The features to be noted include short stature, dislocated hips, microcephaly, a broad nasal base, epicanthal folds, micrognathia, thumbs attached by a thread, and café-au-lait spots with hypopigmented areas beneath. (From Nathan DC, Orkin SH, Ginsburg D, et al, editors: Nathan and Oski’s hematology of infancy and childhood, ed 6, vol I, Philadelphia, 2003, WB Saunders, p. 285.)
Laboratory Findings
Marrow failure usually ensues in the 1st decade of life. Thrombocytopenia and red blood cell macrocytosis often appears initially, with subsequent onset of granulocytopenia and then anemia. Severe aplasia develops in most cases, but its full expression is variable and evolves over a period of months to years. The marrow becomes progressively hypocellular and fatty, like that in severe acquired aplastic anemia. Chromosome fragility is indicated by spontaneously occurring chromatid breaks, rearrangements, gaps, endoreduplications, and chromatid exchanges in blood lymphocytes cultured with phytohemagglutinin as well as in cultured skin fibroblasts, underscoring the constitutional nature of the disorder. With addition of DEB or mitomycin C, fragility is strikingly enhanced in lymphocyte cultures of patients with FA in comparison with those of controls. For prenatal diagnosis, abnormal chromosome breakage analysis and genetic testing can be performed in amniotic fluid cells or in tissue from a chorionic villus biopsy.

Complications
In addition to the low blood counts and physical anomalies, a major feature of the phenotype of FA is the propensity for cancer. The most frequent solid tumors are squamous cell carcinomas of the head, neck, and upper esophagus, followed by carcinomas of the vulva and/or anus, cervix, and lower esophagus. Human papilloma virus is suspected in the pathogenesis. Some patients experience oral cancer after bone marrow transplantation; it is unclear whether this treatment has an effect on the incidence. Benign and malignant liver tumors occur (adenomas, hepatomas) are usually associated with androgen therapy for aplastic anemia. Androgens are also implicated in the etiology of peliosis hepatis (blood-filled hepatic sinusoids). Peliosis hepatis is reversible when androgen therapy is discontinued, and tumors may regress. Clonal marrow cytogenetic abnormalities are common in FA, and at follow-up can either be stable, intermittently detected, or progressive and develop to advanced MDS and acute myelogenous leukemia. Approximately 15% of patients with FA are at risk for acute leukemia by the age of 35 yr.

Diagnosis
FA should be considered in all children and young adults with unexplained cytopenias. Abnormal hematologic findings and characteristic physical anomalies suggest the diagnosis, which is confirmed with a lymphocyte chromosomal breakage study using DEB. No other inherited pancytopenia is associated with a prominent in vitro hypersensitivity to DEB or mitomycin C by the chromosomal breakage study. Ten percent to 15% of patients with suspected FA have “somatic mosaicism” and their lymphocytes may not show characteristic high level of chromosomal fragility because of mixed populations of somatic cells, some with 2 abnormal alleles and some with 1 (caused by spontaneous somatic gene correction in a portion of the cells). Testing of skin fibroblasts instead of lymphocytes confirms the diagnosis. Most patients have stable elevations of serum α-fetoprotein expressed constitutively, independent of liver complications or androgen therapy. Because of its low specificity compared to the chromosomal fragility and molecular tests the laboratory measurement of serum α-fetoprotein has not been widely used as a screening test.

As a result of the large number of FANC genes, genetic diagnosis has traditionally been commenced with complementation testing. This is done by determining whether cellular hypersensitivity to crosslinking agents (e.g., mitomycin C or radiation) or immunoblotting for FANCD2 is restored after generating hybridoma of the patient cells with known genetic complementation cells or after transducing the cells with a known FANC gene. The mutant gene or the complementation group is deduced when a specific wild-type FANC gene corrects the abnormal chromosomal fragility.

Treatment
A hematologist and a multidisciplinary team should supervise patients with FA. If the hematologic findings are stable and there are no transfusion requirements, observation is indicated. Subspecialty consultations for anomalies and disabilities can be arranged during this interval. If growth velocity is below expectations, endocrine evaluation is needed to identify growth hormone deficiency or hypothyroidism. Screening for glucose intolerance and hyperinsulinemia should be performed annually or biannually, depending on the degree of hyperglycemia found on initial testing. Blood counts should be performed every 1-3 mo; bone marrow aspiration and biopsy are indicated annually for leukemia and MDS surveillance by means of morphology and cytogenetics. Patients should be assessed for solid tumors at least annually. Beginning at adolescence, female patients should be screened annually for gynecologic cancer. Administration of human papilloma virus quadrivalent vaccine to prevent squamous cell carcinoma is currently advised.

Hematopoietic stem cell transplantation (HSCT; see Chapter 135) is the only curative therapy for the hematologic abnormalities. Patients <10 yr old with FA who undergo transplantation using an human leukocyte antigen (HLA)-identical sibling donor have a survival rate >80%. Survival rates are lower for patients >10 yr old who are undergoing the procedure. Preparative regimens are continuously evaluated, refined, and improved worldwide. For patients who do not have an HLA-matched sibling donor, a search for a matched unrelated donor (including a search of umbilical cord blood banks) might be initiated. Because of the need for more intensive preparation regimen and the heightened graft-versus-host response in patients with FA, the survival and cure rates have not been as good as those for matched sibling donor HSCT (=50% survival). Molecular technology has led to preplantation genetic diagnosis on parent-derived blastomers to find an HLA-matched sibling donor without FA.

Androgens produce a response in 50% of patients, heralded by reticulocytosis and a rise in hemoglobin within 1-2 mo. White blood cell counts may increase next, followed by platelet counts, but it may take many months to achieve the maximum response. When the response plateaus, androgen dosage can be slowly tapered but not stopped entirely. Oral oxymetholone is used most frequently once a day. The beneficial effect of adding low-dose prednisone to androgens is controversial, but when administered orally every second day, they may counter androgen-induced growth acceleration and prevent thrombocytopenic bleeding by promoting vascular stability. In many patients who are taking androgens, the disease becomes refractory as marrow failure progresses. Potential side effects include masculinization, elevated hepatic enzymes, cholestasis, peliosis hepatitis, and liver tumors. Screening for these changes should be performed serially.

The potential for recombinant growth factor (cytokine) therapy for FA has not been defined. Granulocyte colony-stimulating factor (G-CSF) can usually induce an increase in the absolute neutrophil count and occasionally may boost platelet counts and hemoglobin levels. There may be a heightened risk of expansion of marrow cells with clonal cytogenetic abnormalities such as monosomy 7. Combining therapy consisting of G-CSF given subcutaneously daily or every 2 days along with erythropoietin given subcutaneously or IV 3 times/wk results in improved neutrophil counts in almost all patients and a sustained rise in platelets and hemoglobin levels in approximately one-third of patients, although most patients lose the response after 1 yr owing to progression of marrow failure.

The premise for gene therapy in FA is based on the assumption that corrected hematopoietic cells offer a growth advantage. Attempts at gene therapy have been disappointing, possibly because of the type of vector but also because of the chromosomal fragility and impaired proliferative function of the hematopoietic progenitors. Encouraging preclinical data from studies using lentiviral vectors offer hope that gene therapy will be a safe and effective treatment for FA.

Prognosis
From FA cases reported in the 1990s, the projected median survival was >30 yr of age, an improvement over that in the previous decade. Successes with HSCT have dramatically improved the outlook. Careful surveillance for known complications, especially cancer, and prompt intervention on their detection has also contributed to the improved survival.
SHWACHMAN-DIAMOND SYNDROME
Etiology and Epidemiology
Shwachman-Diamond syndrome (SDS) is inherited in an autosomal recessive manner; it occurs in all racial and ethnic groups. As FA, SDS is also a multisystem disorder. The nonhematologic manifestations are different and usually include exocrine pancreatic insufficiency and skeletal abnormalities such as metaphyseal dysplasia. There is no increased chromosomal breakage after DEB testing of SDS lymphocytes.

Pathology
The mutant gene SDRS maps to chromosome 7q11 and in 90% of cases is responsible for the multisystem, pleiotropic phenotype. The wild-type gene protein product is involved in ribosomal biogenesis. Pancreatic insufficiency is a result of failure of pancreatic acinar development. Fatty replacement of pancreatic tissue is prominent. Bone marrow failure is characterized by dysfunctional hematopoietic stem cells, accelerated apoptosis of marrow progenitors and a defective marrow microenvironment that does not support and maintain normal hematopoiesis.

Clinical Manifestations
Most patients with SDS have symptoms of fat malabsorption from birth that are caused by pancreatic insufficiency, but steatorrhea is not always obvious. Approximately 50% of patients appear to exhibit an improvement in pancreatic enzyme secretion as they age. The clinical picture can be dominated by complications from anemia, neutropenia, or thrombocytopenia. Bacterial and fungal infections secondary to neutropenia, neutrophil dysfunction, and immune deficiency can occur. Short stature is a consistent feature of the syndrome; most patients show normal growth velocity yet remain consistently below the 3rd percentile for height and weight. The occasional SDS adult achieves the 25th percentile for height. Although skeletal abnormalities are variable, classic findings are delayed bone maturation, metaphyseal dysplasia, short or flared ribs, and thoracic dystrophy. Some patients have hepatomegaly and elevations of liver enzymes. Most patients have dental abnormalities and poor oral health. Many have neurocognitive problems and poor social skills.

Laboratory Findings
Fatty replacement of pancreatic tissue can be visualized by CT scan or ultrasound. Fat malabsorption is proven by assay on a 72-hr stool collection. Pancreatic function tests show markedly impaired enzyme secretion, but with preservation of ductal function. Age-adjusted serum trypsinogen and isoamylase levels are reduced. Neutropenia is present in 100% of patients with SDS on at least 1 occasion. It can be chronic persistent or intermittent. It has been identified in some neonates during an episode of sepsis. Neutrophils may have a defect in mobility, migration, and chemotaxis owing to alterations in neutrophil cytoskeletal or microtubular function. Anemia, thrombocytopenia, and pancytopenia are seen in 66%, 60%, and up to 44% of cases, respectively. Pancytopenia can be severe as a result of full-blown aplastic anemia. Bone marrow biopsy specimens and aspirates usually show varying degrees of marrow hypoplasia and fat infiltration. Patients may also have B-cell defects with 1 or more of the following: low immunoglobulin G or immunoglobulin G subclasses, low percentage of circulating B lymphocytes, decreased in vitro B-cell proliferation, and lack of specific antibody production. Patients may have a low percentage of circulating T cells, subsets, or natural killer cells, and decreased in vitro T-cell proliferation.

Diagnosis
The clinical diagnosis of SDS relies on having an evidence of bone marrow dysfunction and exocrine pancreatic dysfunction. However, up to 20% of the patients may lack clear evidence of exocrine pancreatic defects at the time of diagnosis. Mutational analysis for SBDS is definitive in 90% of cases. Pearson syndrome (see Chapter 450), consisting of refractory sideroblastic anemia, cytoplasmic vacuolization of bone marrow precursors, lactic acidosis, exocrine pancreatic insufficiency, and a diagnostic mitochondrial DNA mutation is similar to SDS, but the clinical course, morphologic features of the bone marrow, and gene mutation are different. Also, severe anemia requiring transfusion, rather than neutropenia, is present from birth to 1 yr of age. SDS shares some manifestations with FA, such as marrow dysfunction and growth failure, but patients with SDS are readily distinguished because of pancreatic insufficiency with fat malabsorption, fatty changes within the pancreatic body that can be visualized by imaging, characteristic skeletal abnormalities not seen in FA, and a normal chromosomal breakage study with DEB.

Complications
Patients with SDS are predisposed to MDS and leukemic transformation. The crude rate of MDS or acute leukemia in patients with SDS is 8-33%. Marrow cell clonal cytogenetic abnormalities are an isolated finding, occurring in up to 41% of patients. Isochromosome 7 [i(7q)] is particularly common, suggesting that it is a fairly specific clonal marker of SDS and probably related to the presence of mutant SBDS on 7q11. Other clonal chromosome abnormalities include monosomy 7, i(7q) combined with monosomy 7, deletions or translocations involving part of 7q, and deletions of 20q [Del(20q)]. Although i(7q) and Del(20q) are rarely related to leukemic transformation or MDS, the prognostic significance of all marrow clonal changes requires prospective monitoring.

Treatment
Fat malabsorption responds to oral pancreatic enzyme replacement and supplemental fat-soluble vitamins, administered according to guidelines similar to those for cystic fibrosis (see Chapter 403). A long-term plan should be initiated to monitor changes in peripheral blood counts that require corrective action and to look for early evidence of malignant myeloid transformation. The latter requires serial bone marrow aspirations for smears and cytogenetics and marrow biopsy. One recommendation is to perform marrow testing every 1-2 yr and complete blood counts every 3 mo.

Daily subcutaneous G-CSF for profound neutropenia is effective in inducing a sustained increase in neutrophils. Some patients require transfusion support for management of severe anemia or thrombocytopenia. Experience with erythropoietin is limited. In some patients who received androgens plus steroids, blood counts have improved. The only curative option for severe marrow failure in SDS is allogeneic HSCT, although experience has been limited. Traditional myeloblastic HSCT resulted in treatment-related mortality in 35-50% of the patients. The risk of cardiotoxicity has been noted. Fludarabine-based protocols using reduced-intensity conditioning appear to be safer and effective for SDS HSCT.

Prognosis
The accurate life expectancy of SDS patients is unknown. Analysis of published cases revealed a median survival of 35 yr. Because the number of undiagnosed patients with mild or asymptomatic disease is unknown, the overall prognosis may be better than previously thought. Approximately 50% of patients experience spontaneous conversion from pancreatic insufficiency to pancreatic sufficiency as a result of improvement in pancreatic enzyme secretion. Enzyme replacement therapy is then no longer needed. Although all patients have some degree of hematologic cytopения, the changes in most patients are mild to moderate and do not require therapeutic intervention. Severe neutropenia responds well to G-CSF, but there is concern that the predisposition to MDS and acute leukemia can be heightened by the agent's powerful growth stimulus on marrow cells. HSCT for severe marrow failure has produced a 50-70% survival rate, but safer protocols are being introduced. Malignant marrow transformation remains ominous.

DYSKERATOSIS CONGENITA
Etiology and Epidemiology
Dyskeratosis congenita (DC) is an inherited multisystem disorder characterized by mucocutaneous abnormalities, bone marrow failure,
and a predisposition to cancer and MDS. The diagnostic mucocutaneous (ectodermal) triad is reticulate skin pigmentation of the upper body, mucosal leukoplakia, and nail dystrophy (Fig. 468-2). Skin and nail findings usually become apparent in the 1st 10 yr of life, whereas oral leukoplakia is seen later. These manifestations tend to progress as patients get older. Varying degrees of bone marrow failure are seen in about 90% of the patients. Severe aplastic anemia occurs in approximately 50% of cases, usually in the 2nd decade of life. Many patients with DC are male, a finding compatible with the high frequency of the X-linked recessive form of the disease. The remainder have either an autosomal dominant or autosomal recessive mode of inheritance.

**Pathology**

DC is genetically heterogeneous, and patients have mutations in genes that encode components of the telomerase complex (DKC1, TERT, TERC, NOP10, and NHP2), T-loop disassembly protein (RTEL1), telomere capping (CTC1), the telomere shelterin complex (TINF2), and the telomerase trafficking protein (TCAB1), all components critical for telomere maintenance. The X-linked recessive form of DC maps to Xq28, and many mutations have been identified in the DKC1 gene, which codes for the nuclear protein dyskerin. The autosomal dominant form is due to mutations in TINF2, or in TERC or TERT, the RNA and enzymatic components of telomerase, respectively. Autosomal recessive DC is linked to mutations in NOP10, NHP2, RTEL1, TCAB1, and CTC1. Because of impaired telomere maintenance in all 3 inherited forms of DC, short telomeres are demonstrated in the peripheral blood cells of all patients and are a cardinal marker for DC and for marrow failure. The failure is likely a result of progressive attrition and depletion of hematopoietic stem cells because of premature senescence, which manifests as pancytopenia.

**Clinical Manifestations**

Skin pigmentation and nail changes typically appear first, mucosal leukoplakia and excessive ocular tearing appear later, and by the mid-teens, patients with DC have bone marrow failure and malignancy. Many female patients have the same features as male patients. In males, cutaneous findings are the most consistent feature. Lacy reticulated skin pigmentation affecting the face, neck, chest, and arms is a common finding (89%). The degree of pigmentation increases with age and can involve the entire skin surface. There may also be a telangiectatic erythematous component. Nail dystrophy of both hands and feet is the next most common finding (88%). It usually starts with longitudinal ridging, splitting, or pterygium formation and may progress to complete nail loss. Leukoplakia usually involves the oral mucosa (78%), especially the tongue but may also be seen in the conjunctiva and the anal, urethral, or genital mucosa. Hyperhidrosis of the palms and soles is common, and hair loss is sometimes seen. Eye abnormalities are observed in approximately 50% of cases. Excessive tearing (epiphora) secondary to nasolacrimal duct obstruction is common. Other ophthalmologic manifestations include conjunctivitis, blepharitis, loss of eyelashes, strabismus, cataracts, and optic atrophy. An increased rate of dental decay and early loss of teeth are common. Skeletal abnormalities, such as osteoporosis, avascular necrosis, abnormal bone trabeculation, scoliosis, and mandibular hypoplasia, are seen in approximately 20% of cases. Genitourinary abnormalities include hypoplastic testes, hypospadias, phimosis, urethral stenosis, and horseshoe kidney. Gastrointestinal findings, such as esophageal strictures, vascular lesions causing bleeding, hepatomegaly, and fibrosis are seen in 10% of cases. A subset of patients has pulmonary complications, with reduced diffusion capacity and/or a restrictive defect. In fatal cases, lung tissue shows pulmonary fibrosis and abnormalities of the pulmonary vasculature.

**Laboratory Findings**

The initial hematologic change in DC is usually thrombocytopenia, anemia, or both, followed by full-blown pancytopenia and aplastic anemia. The red cells are often macrocytic, and the fetal hemoglobin value can be elevated initially. Initial bone marrow specimens may be hypercellular, but with time, a symmetric depletion of all hematopoietic lineages ensues. Some patients have immunologic abnormalities, including reduced or elevated immunoglobulin values, decreased B- and/or T-lymphocyte count, and reduction of or absence of lymphocyte proliferative responses to phytohemagglutinin. This is particularly common and severe in the DKC1-associated disease. Primary skin
fibroblasts in culture have abnormal morphologic features and doubling rate and show numerous unbalanced chromosome rearrangements, such as dicentrics, triradials, and translocations, in the absence of DEB. These findings provide evidence of a defect that predisposes patient cells to chromosomal rearrangements and possibly to DNA damage.

**Diagnosis**
The following abnormalities are seen in patients with DC but not in those with FA: nail dystrophy, leukoplakia, and tooth abnormalities, hyperhidrosis of the palms and soles, and hair loss (see Table 468-2).

There are overlap syndromes that share some of the features of DC. **Hoyeraal-Hreidarsson syndrome** is a multisystem disorder comprising aplastic anemia, immunodeficiency, microcephaly, growth retardation, and cerebellar hypoplasia. The syndrome is genetically heterogeneous; some cases are X-linked recessive and caused by mutations in **DKC1**, and others are autosomal recessive owing to homozygous **TERT** mutations. **Revesz syndrome** consists of dystrophic nails, leukoplakia, aplastic anemia, cerebellar hypoplasia, growth retardation, microcephaly, and bilateral exudative retinopathy. **TINF2** is mutated in Revesz syndrome, which hence is an autosomal dominant variant of DC. Coats’ plus syndrome is caused by mutations in the **CTCI** gene. It is characterized by retinal telangiectasia and exudates, intracranial calcification, leukodystrophy, brain cysts, osteopenia, gastrointestinal bleeding and portal hypertension caused by the development of vasculature ectasias in the stomach, small intestine and liver. Some patients with this disease has the additional manifestations of DC, which include sparse and graying hair, dystrophic nails, and anemia. Telomeres are short.

**Complications**
Cancer develops in approximately 10-15% of patients with DC, usually in the 3rd and 4th decades of life. Patients with DC are predisposed to MDS as well as to solid tumors. Forty percent of the cancers in such patients are squamous cell carcinomas of the head and neck (tongue, mouth, pharynx). Cancer of the skin and gastrointestinal tract (esophagus, stomach, colon, and especially the anorectal site) is also common. Other life-threatening complications include pulmonary fibrosis and severe gastrointestinal bleeding.

**Treatment**
Androgens (with or without low-dose prednisone) can induce improvement of marrow function in approximately 50% of patients. When the response is maximal, the androgen dose can be slowly tapered but not stopped. DC can become refractory to androgens as the aplastic anemia progresses. There is no published information on the use of immunosuppressive therapy for this disorder, but the authors are aware of several patients who were misdiagnosed with acquired aplastic anemia and treated with immunosuppressive therapy without response. Although reports are scanty, cytokine therapy with granulocyte-macrophage colony-stimulating factor or with G-CSF alone or combined with erythropoietin appears to offer potential benefit, at least in the short term, especially for improving neutrophil numbers.

Allogeneic HSCT has been used to correct marrow failure in patients with DC, long-term survival is only 50%. Vascular lesions and fibrosis involving various organs are not prevented by HSCT and can occur early and late after transplantation; carrying a high mortality rate. Patients with DC may be more susceptible to endothelial damage that occurs after HSCT as a result of various factors, including the conditioning regimen, infectious disease, and graft-versus-host disease. Up to 40% of patients with DC experience fatal pulmonary complications after transplantation.

**Prognosis**
Considerable heterogeneity exists in DC. Patients with certain genetic groups (e.g., **TERTC** and **TERT**) have milder clinical manifestations. Patients with other genetic groups (e.g., **DKC1, TINF2** and **RTEL1**) appear to have more physical anomalies and a higher incidence of aplastic anemia and cancer. The mean age of death for patients with DC who are diagnosed in childhood is approximately 30 yr. The main causes of death are bone marrow failure, complications of HSCT, cancer, fatal pulmonary problems, and gastrointestinal bleeding.

**CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA**

**Etiology and Epidemiology**
Congenital amegakaryocytic thrombocytopenia (CAMT) is the rarest of the 4 major inherited pancytopenias. It is transmitted in an autosomal recessive manner. CAMT manifests in infancy as isolated thrombocytopenia as a result of reduction or absence of marrow megakaryocytes with initial preservation of granulopoietic and erythropoietic lineages. Panthoerythropoiesis caused by aplastic anemia often ensues in the first few years of life. The defect in CAMT is directly related to mutations in **MPL**, the gene for the receptor of thrombopoietin, the growth factor that promotes hematopoietic stem cell survival and stimulates megakaryocyte proliferation and maturation. Carriers of the mutant gene have normal hematology; affected individuals have mutations in both alleles. Genotype-phenotype correlations predict disease course and prognosis. **Nonsense mutations** cause a complete loss of function of the thrombopoietin receptor, causing persistently low platelet counts because of the absence of megakaryocytes and a fast progression to pancytopenia and aplastic anemia (CAMT type I). Because thrombopoietin also has an antiapoptotic and cell survival effect on stem cells, impaired stem cell survival with **MPL** nonsense mutations explains the evolution of CAMT into aplastic anemia. **Missense mutations** of **MPL** are associated with a milder course, a transient increase in platelets during the 1st yr of life, and delayed onset, if any, of pancytopenia, indicating residual receptor function (CAMT type II). Biologically active plasma thrombopoietin is consistently elevated in all patients with CAMT.

**Clinical Manifestations**
Patients with CAMT have petechial rash, bruising, or bleeding at birth or in the 1st yr of life. Most, but not all, patients with proven **MPL** mutations have normal physical and imaging features. Approximately 20% of published phenotypic CAMT cases involved physical anomalies, but **MPL** mutation analyses were not available in all cases. The most common anomalies in the published cases are neurologic and cardiac. Findings related to cerebellar and cerebral atrophy are frequent, and developmental delay is a prominent feature. Congenital heart disease includes atrial septal defects, ventricular septal defects, patent ductus arteriosus, tetralogy of Fallot, and coarctation of the aorta. Some of these occur in combinations. Other anomalies include abnormal hips or feet, kidney malformations, eye anomalies, and cleft or high-arched palate. Some patients have microcephaly and an abnormal facies.

**Laboratory Findings**
Thrombocytopenia is the major laboratory finding in CAMT, with normal hemoglobin levels and white blood cell counts initially. Peripheral blood platelets are reduced or totally absent. As in other inherited bone marrow failure syndromes, red blood cells may be macrocytic. Hemoglobin F may be elevated, and there may be increased expression of i antigen. Initial bone marrow aspirates and biopsy specimens show normal cellularity with marked reduction or absence of megakaryocytes. In patients in whom aplastic anemia develops, marrow cellularity is decreased, with fatty replacement; erythropoietic and granulopoietic lineages are also symmetrically reduced.

**Diagnosis**
If thrombocytopenia persists beyond the neonatal period or is associated with adequate platelet transfusion response and no obvious precipitating cause such as infections or immunologic reactions, a marrow aspirate and biopsy is indicated. Deficient megakaryocytes in such cases suggest the diagnosis, and mutational analysis will confirm it. If CAMT occurs at birth or shortly after, it must be distinguished from other causes of inherited and acquired neonatal thrombocytopenia (see Chapter 484.8). Thrombocytopenia with absent radii (TAR syndrome) is distinguished from CAMT because in TAR syndrome the
radii are absent. The distinction from DC may be evident by mucocutaneous, neurologic, and immunologic findings that are characteristic to the early onset DC. CAMT blood lymphocytes do not show increased chromosomal breakage when exposed to DEB, distinguishing the disease it from FA.

Complications
In some patients, clonal marrow cell cytogenetic abnormalities appear such as monosomy 7 and trisomy 8. CAMT can evolve into MDS and also acute leukemia, but the true risk cannot be defined because of the rarity of the disease and the paucity of published data.

Therapy and Prognosis
The mortality rate in patients with MPL nonsense mutations from thrombocytopenic bleeding, complications of aplastic anemia, or leukemic transformation has been very close to 100%. Patients with nonsense mutations have a milder course but may still have serious complications. HSCT is the only curative option. The majority of patients with CAMT who undergo HSCT are cured, especially if the procedure is performed with HLA-matched sibling donors. Before transplantation, platelet transfusion should be used discretely. Platelet count should not always be the sole indication; clinical bleeding is an appropriate trigger. Single-donor filtered platelets are preferred to minimize sensitization. Leukodepleted platelet units might be adequate, but further studies are necessary to support such an alternative. In a patient for whom HSCT is a possibility, all blood products should be free of cytomegalovirus. Corticosteroids are not effective for treatment of the thrombocytopenia. For aplastic anemia, androgens may induce a temporary partial improvement. Interleukin-3 may be an important adjunct to the medical management of CAMT, but it was not adopted broadly and is no longer available. The role of thrombomimetic agents has to be studied; however, the induction of fibrosis by these agents and the risk of MDS/leukemia in CAMT render HSCT the preferred treatment for patients with severe cytopenia.

OTHER INHERITED SYNDROMES
Pancytopenia and bone marrow failure can occur in the context of several non-hematologic syndromes and familial settings that do not exactly correspond to the entities already described.

Down Syndrome
Down syndrome (trisomy 21; see Chapter 81.2) has a unique association with aberrant hematologic findings. In addition to the propensity for acute lymphoblastic and myeloblastic leukemias, especially acute megakaryoblastic leukemia, at least 6 patients with Down syndrome have been reported as having pancytopenia caused by aplastic anemia.

Dubowitz Syndrome
Dubowitz syndrome is an autosomal recessive disorder characterized by a peculiar facies, infantile eczema, small stature, and mild microcephaly. The face is small, with a shallow supraorbital ridge, a nasal bridge at the same level as the forehead, short palpebral fissures, variable ptosis, and micrognathia. There is a predilection to cancer as well as to bone marrow dysfunction in these patients. Approximately 10% of patients have hematopoietic disorders including moderate pancytopenia, hypoplastic anemia, bone marrow hypoplasia, and full-blown aplastic anemia. No gene mutation has been identified.

Seckel Syndrome
Seckel (SCKL) syndrome, sometimes called “bird-headed dwarfism,” is an autosomal recessive developmental disorder characterized by marked growth failure and mental deficiency, microcephaly, a hypoplastic face with a prominent nose, and low-set and/or malformed ears. Approximately 25% of patients have aplastic anemia or malignancies. There is broad genetic heterogeneity comprising 7 classifiable types: SCKL1, ATR mutation; SCKL2, RBBP8 mutation; SCKL3, maps to 14q21-q22; SCKL4, CENP1 mutation; SCKL5, CEP152 mutation; SCKL6, CEP63 mutation; and, SCKL7, NIN mutation.

Reticular Dysgenesis
Reticular dysgenesis (see Chapter 126) is an immunologic deficiency syndrome coupled with congenital agranulocytosis. The mode of inheritance autosomal recessive in some cases; there is evidence that reticular dysgenesis is caused by homozygous or compound heterozygous mutation in the mitochondrial adenyate kinase-2 gene AK2 on chromosome 1p35 but an X-linked mode is also possible in some cases. The disorder is a variant of severe combined immune deficiency in which cellular and humoral immunity are absent and severe lymphopenia and neutropenia are also seen. Anemia and thrombocytopenia may also be present. Bone marrow specimens are hypocellular, with markedly reduced myeloid and lymphoid elements. The only curative therapy is HSCT.

Schimke Immunooosseous Dysplasia
Schimke immunooosseous dysplasia is an autosomal recessive disorder caused by mutations in the chromatin remodeling protein SMARCAL1. Patients have spondyloepiphyseal dysplasia with exaggerated lumbar lordosis and a protruding abdomen. There are pigmentary skin changes and abnormally discolored and configured teeth. Renal dysfunction can be problematic, with proteinuria and nephrotic syndrome. Approximately 50% of patients have hypothyroidism, 50% have cerebral ischemia, and 10% have bone marrow failure with neutropenia, thrombocytopenia, and anemia, and about 5% are predisposed to non-Hodgkin lymphoma. Lymphopenia and altered cellular immunity are present in almost all patients. In 2 published case reports, 2 patients underwent successful bone marrow transplantation.

Noonan Syndrome
Noonan syndrome is a developmental disorder characterized by the “Noonan facies” (hypertelorism, ptosis, short neck, low-set ears), short stature, congenital heart disease, and multiple skeletal and hematologic abnormalities. It is primarily an autosomal dominant disorder composed of at least 7 genetic types. Heterozygous mutations in PTPN11 cause approximately 50% of cases of the syndrome; others are caused by mutations in NF1, KRAS, SOS1, RAF1, NRAS, or BRAF. Autosomal recessive forms have also been identified due to a mutation of SHOC2 or of CBL. In addition to an association with juvenile myelomonocytic leukemia, Noonan syndrome patients can develop amegakaryocytic thrombocytopenia as well as pancytopenia with a hypocellular marrow.

Cartilage-Hair Hypoplasia
Cartilage-hair hypoplasia, an autosomal recessive syndrome seen mostly in Finnish or Amish populations, is characterized by metaphyseal dysostosis, short-limbed dwarfism, and fine, sparse hair. Additional skeletal findings are scoliosis, lordosis, chest deformity, and varus lower limbs. Gastrointestinal abnormalities also occur. Mutations in the RMRP gene cause cartilage-hair hypoplasia. Macrocytic anemia is seen in most patients and is sometimes severe and persistent. Neutropenia, lymphopenia, and a predisposition to lymphoma and other cancers are also features.

UNCLASSIFIED INHERITED BONE MARROW FAILURE SYNDROMES
Unclassified inherited bone marrow failure syndromes are heterogeneous disorders that may be either atypical presentations of identifiable diseases or new syndromes. Characterized by various cytopenias because of underproductive bone marrow with or without physical manifestations, they do not fit into a classic genetic bone marrow failure disease because all features may not be evident at the time of presentation. Compared with classic disorders (presentation >1 mo of age), infants with unclassified disorders present later (>9 mo) and manifest single or multiligneage cytopenia, aplastic anemia, myelodysplasia, or malignancy with variable expression of malformations. Table 468-4 lists the criteria for the diagnosis. With follow-up, some may demonstrate typical physical features of known syndromes, such as SDS, although without obvious mutations in the SBDS gene.
Table 468-4  
Canadian Inherited Marrow Failure Registry Criteria for Unclassified Inherited Bone Marrow Failure Syndromes

<table>
<thead>
<tr>
<th>FULFILLS CRITERIA 1 AND 2:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does not fulfill criteria for any categorized inherited bone marrow failure syndrome*</td>
<td></td>
</tr>
<tr>
<td>2. Fulfills both of the following</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FULFILLS AT LEAST 2 OF THE FOLLOWING:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Chronic cytopenia(s) detected on at least 2 occasions over at least 3 mo†</td>
<td></td>
</tr>
<tr>
<td>b. Reduced marrow progenitors or reduced clonogenic potential of hematopoietic progenitor cells or evidence of ineffective hematopoiesis‡</td>
<td></td>
</tr>
<tr>
<td>c. High fetal hemoglobin for age‡</td>
<td></td>
</tr>
<tr>
<td>d. Red blood cell macrocytosis (not caused by hemolysis or a nutritional deficiency)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FULFILLS AT LEAST 1 OF THE FOLLOWING:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Family history of bone marrow failure</td>
<td></td>
</tr>
<tr>
<td>b. Presentation at age &lt;1 yr</td>
<td></td>
</tr>
<tr>
<td>c. Anomalies involving multiple systems to suggest an inherited syndrome</td>
<td></td>
</tr>
</tbody>
</table>

*The Canadian Inherited Marrow Failure Registry diagnostic guidelines for selected syndromes were adapted from the literature and are available at http://www.sickkids.ca/cimfr.

†Cytopenia was defined as follows: neutropenia, neutrophil count of <1.5 x 10^9/L; thrombocytopenia, platelet count of <150 x 10^9/L; anemia, hemoglobin concentration of <2 standard deviations below mean, adjusted for age.

‡Hemoglobinopathies with ineffective erythropoiesis and high hemoglobin F should be excluded by clinical or laboratory testing.

Familial cases with aplastic anemia that cannot be readily classified into discrete diagnostic entities such as FA have been reported. When the patients present not early after birth and without physical malformations an acquired etiology cannot be ruled out. Detailed genetic testing for known inherited bone marrow failure syndrome genes or by whole exome or genome sequencing may identify an inherited etiology.

Bibliography is available at Expert Consult.
Bibliography


ETIOLOGY AND EPIDEMIOLOGY
Drugs, chemicals, toxins, infectious agents, radiation, and immune disorders can result in pancytopenia by direct destruction of hematopoietic progenitors, disruption of the marrow microenvironment, or immune-mediated suppression of marrow elements (Table 469-1). A careful history of exposure to known risk factors should be obtained for every child presenting with pancytopenia. Even in the absence of the classic associated physical findings, the possibility of a genetic predisposition to bone marrow failure should always be considered (see Chapter 468). The majority of cases of acquired marrow failure in childhood are “idiopathic,” in that no causative agent is identified. Many are probably immune-mediated through activated T lymphocytes and cytokine destruction of marrow progenitor cells. The overall incidence of acquired aplastic anemia is relatively low, with an approximate incidence in both children and adults in the United States and Europe of 2-6 cases/million population/yr. The incidence is higher in Asia, with as many as 14 cases/million population/yr in Japan.

Severe bone marrow suppression can develop after exposure to many different drugs and chemicals, including certain chemotherapeutic agents, insecticides, antibiotics, anticonvulsants, nonsteroidal antiinflammatory agents, and recreational drugs. Some of the most notable agents are benzene, chloramphenicol, gold, and, 3,4-methylenedioxymethamphetamine (Ecstasy).

A number of viruses can either directly or indirectly result in bone marrow failure. Parvovirus B19 is classically associated with isolated red blood cell aplasia, but in patients with sickle cell disease or immunodeficiency, it can result in transient pancytopenia (see Chapter 251). Prolonged pancytopenia can occur after infection with many of the hepatitis viruses, herpes viruses, Epstein-Barr virus (see Chapter 254), cytomegalovirus (see Chapter 255), and HIV (see Chapter 276).

Patients with evidence of bone marrow failure should also be evaluated for inherited forms of marrow failure, paroxysmal nocturnal hemoglobinuria (PNH; see Chapter 464), and collagen vascular diseases. Pancytopenia without peripheral blasts may be caused by bone marrow replacement by leukemic blasts or neuroblastoma cells.

PATHEOLOGY AND PATHOGENESIS
The hallmark of aplastic anemia is peripheral pancytopenia, coupled with hypoplastic or aplastic bone marrow. The severity of the clinical course is related to the degree of myelosuppression. Severe aplastic anemia is defined as a condition in which 2 or more cell components have become seriously compromised (absolute neutrophil count <500/mm³, platelet count <20,000/mm³, reticulocyte count <1% after correction for hematocrit) in a patient whose bone marrow biopsy material is moderately or severely hypocellular. Approximately 65% of patients who first present with moderate aplastic anemia (absolute neutrophil count 500-1,500/mm³, platelet count 20,000-100,000/mm³, reticulocyte count <1%) eventually progress to meet the criteria for severe disease, if they are simply observed. Bone marrow failure may be a consequence of a direct cytotoxic effect on hematopoietic stem cells from a drug or chemical or may result from either cell-mediated or antibody-dependent cytotoxicity. There is strong evidence that many cases of idiopathic aplastic anemia are caused by an immune-mediated process, with increased circulating activated T lymphocytes producing cytokines (interferon-γ) that suppress hematopoiesis. Abnormal telomere

Table 469-1  Etiology of Acquired Aplastic Anemia
<table>
<thead>
<tr>
<th>Etiology of Acquired Aplastic Anemia</th>
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</thead>
<tbody>
<tr>
<td>Radiation, drugs, and chemicals:</td>
</tr>
<tr>
<td>Predictable: chemotherapy, benzene</td>
</tr>
<tr>
<td>Idiosyncratic: chloramphenicol, antiepileptics, gold, 3,4-methylenedioxymethamphetamine</td>
</tr>
<tr>
<td>Viruses:</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Epstein-Barr</td>
</tr>
<tr>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Hepatitis non-A, non-B, non-C (seronegative hepatitis)</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Immune diseases:</td>
</tr>
<tr>
<td>Eosinophilic fasciitis</td>
</tr>
<tr>
<td>Hypoimmunoglobulinemia</td>
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<tr>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
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<tr>
<td>Marrow replacement:</td>
</tr>
<tr>
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</tr>
<tr>
<td>Myelodysplasia</td>
</tr>
<tr>
<td>Myelofibrosis</td>
</tr>
<tr>
<td>Autoimmune</td>
</tr>
<tr>
<td>Other:</td>
</tr>
<tr>
<td>Cryptic dyskeratosis congenita (no physical stigmata)</td>
</tr>
<tr>
<td>Telomerase reverse transcriptase haploinsufficiency</td>
</tr>
</tbody>
</table>
length and telomerase activity in granulocytic precursors and increased expression of cell surface Flt3 ligand (a member of the class III receptor tyrosine kinase family) in the lymphocytes of patients with aplastic anemia suggest that early apoptosis of hematopoietic progenitors may play a role in the pathogenesis of this disease.

**CLINICAL MANIFESTATIONS, LABORATORY FINDINGS, AND DIFFERENTIAL DIAGNOSIS**

Pancytopenia results in increased risks of cardiac failure, infection, bleeding, and fatigue. Acquired pancytopenia is typically characterized by anemia, leukopenia, and thrombocytopenia in the setting of elevated serum cytokine values. Other treatable disorders, such as cancer, collagen vascular disorders, PNH, and infections that may respond to specific therapies (IV immune globulin for parvovirus), should be considered in the differential diagnosis. Careful examination of the peripheral blood smear for red blood cell, leukocyte, and platelet morphologic features is important. A reticulocyte count should be performed to assess erythropoietic activity. In children, the possibility of congenital pancytopenia must always be considered, and chromosomal breakage analysis should be performed to evaluate for Fanconi anemia (see Chapter 468). The presence of fetal hemoglobin suggests congenital pancytopenia but is not diagnostic. To assess for the possibility of PNH, flow cytometric analysis of erythrocytes for CD55 and CD59 is the most sensitive test. Bone marrow examination should include both aspiration and a biopsy, and the marrow should be carefully evaluated for morphologic features, cellularity, and cytogenetic abnormalities.

**TREATMENT**

The treatment of children with acquired pancytopenia requires comprehensive supportive care coupled with an attempt to treat the underlying marrow failure. For patients with an human leukocyte antigen–identical family member donor, allogeneic hematopoietic stem cell transplantation (HSCT) offers a 90% chance of long-term survival. The typical preparative regimen today consists of cyclophosphamide, fludarabine, and horse antithymocyte globulin (ATG). The risks associated with this approach include the immediate complications of transplantation, graft failure, and graft versus host disease. Late adverse effects associated with transplantation may include secondary cancers, cataracts, short stature, hypothyroidism, and gonadal dysfunction (see Chapters 136–139). Only 1 in 5 patients has a human leukocyte antigen–matched sibling donor, so matched-related HSCT is not an option for the majority of patients.

For patients without a sibling donor, the major form of therapy is immunosuppression with horse ATG and cyclosporine, with a response rate of 70–80%. The median time to response is 6 mo. As many as 30% of responders experience relapse after discontinuation of immunosuppression, and some patients must continue cyclosporine for several years to maintain a hematologic response. Among those who relapse after immunosuppression, approximately 50% show response to a second course of ATG and cyclosporine. There is an increased risk (<10%) of clonal bone marrow disease, such as leukemia, myelodysplasia (MDS), or PNH after immunosuppression with karyotypic abnormalities most frequently involving chromosomes 6, 7, and 8. To accelerate neutrophil recovery, a hematopoietic colony-stimulating factor (e.g., granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor) is sometimes added to ATG and cyclosporine for treatment of patients with very severe neutropenia (absolute neutrophil count <200/mm³), but there is no clear evidence that this treatment influences response rate or survival. In a few cases, tacrolimus has been given successfully with ATG for treatment of aplastic anemia in patients unable to tolerate cyclosporine. Higher baseline reticulocyte count correlates with a higher probability of response to immunosuppression and survival. There is an inverse correlation between telomere length and the probability of relapse post-immunosuppression.

For patients who show no response to immunosuppression or who experience relapse after immunosuppression, matched unrelated HSCT and T-cell depleted haploidentical family member donor HSCT are treatment options, with a response rate approaching 90%. Cord blood transplants have been carried out in this refractory group of patients but there is a significant incidence of non-engraftment. High-dose cyclophosphamide has been used successfully in the treatment of patients with newly diagnosed aplastic anemia and in patients without adequate response to immunosuppression. This therapy leads to prolonged severe pancytopenia, increasing the risk of life-threatening infection, especially fungal. Other therapies that have been used in the past with inconsistent results include androgens, corticosteroids, and plasmapheresis. However, preliminary studies with eltrombopag (an oral thrombopoietin mimetic agent) have resulted in a hematologic response with improvements in platelet and neutrophil counts and hemoglobin levels in some patients. In patients who responded, bone marrow biopsies demonstrated trilineage normalization of hematopoiesis; some who were dependent on platelet or erythrocyte transfusions no longer needed transfusions.

**COMPLICATIONS**

The major complications of severe pancytopenia are predominantly related to the risk of life-threatening bleeding from prolonged thrombocytopenia or to infection secondary to protracted neutropenia. Patients with protracted neutropenia as a result of bone marrow failure are at risk not only for serious bacterial infections but also for invasive mycoses. Patients who have been transfused with red blood cells regularly over a long period are at increased risk of developing alloantibodies to red cell antigens and may require iron chelation therapy for transfusional iron overload. The general principles of supportive care that have evolved from the use of chemotherapy-related myelosuppression to treat patients with cancer should be fully extended to the care of patients with acquired pancytopenia.

**PROGNOSIS**

Spontaneous recovery from pancytopenia rarely occurs. If left untreated, pancytopenia has an overall mortality rate of approximately 50% within 6 mo of diagnosis and of >75% overall, with infection and hemorrhage being the major causes of morbidity and mortality. The majority of children with acquired severe aplastic anemia show response to allogeneic marrow transplantation or immunosuppression, leaving them with normal or near-normal blood cell counts.

**PANCYTOPENIA CAUSED BY MARROW REPLACEMENT**

Processes that either infiltrate or replace the bone marrow can manifest as acquired pancytopenia. Infiltration can be caused by malignancy (classically, neuroblastoma or leukemia) or occur as a consequence of myelofibrosis, MDS, or osteoporosis. Although uncommon, evidence of hypoplastic anemia can precede the onset of acute leukemia, generally by a few months. This relationship is important to appreciate in evaluating and monitoring children who present with what appears to be acquired aplastic anemia. Morphologic examination of the peripheral blood and bone marrow and marrow cytogenetic studies are critically important in making the diagnoses of leukemia, myelofibrosis, and MDS.

MDS is very rare in children, but when it occurs, its clinical course is more aggressive than the same category of MDS in adults. Pediatric MDS can be subdivided into refractory cytopenia of childhood (peripheral blasts <2% and marrow blasts <5%), refractory anemia with excess blasts (peripheral blasts 2-19% and/or marrow blasts 5-19%), and refractory anemia with excess blasts in transformation (peripheral and/or marrow blasts 20-29%). Disease in children with >30% blasts is usually defined as acute myelocytic leukemia.

A number of inherited conditions are associated with an increased risk for development of MDS, including Down syndrome, severe congenital neutropenia, Noonan syndrome, Fanconi anemia, trisomy 8 mosaicism, neurofibromatosis, and Shwachman syndrome. Significant clonal abnormalities are found within the marrow of approximately 50% of patients with MDS, with monosomy 7 and being most common but prognostically neutral. Those with a structurally complex karyotype have a very poor outcome.
The transition time from pediatric MDS to acute leukemia is relatively short, at 14-26 mo, so aggressive treatment, such as HSCT, must be considered shortly after diagnosis. With allogeneic HSCT, the survival rate is approximately 60%. One exception to such an aggressive therapeutic approach is MDS and acute myelocytic leukemia in children with Down syndrome, because this disease in this specific population is very responsive to conventional chemotherapy, with long-term survival rates >80%.

The decision on how to treat a child with MDS who lacks a suitable hematopoietic stem cell donor should be made with the specific clonal abnormality found within the child's marrow taken into consideration. Lenalidomide produces the best responses among patients who have the chromosomal abnormality, 5q−. Immunosuppressive therapy with ATG and cyclosporine is most effective in patients with trisomy 8, especially in the presence of a PNH clone. Imatinib mesylate targets mutations in the tyrosine kinase receptor family of genes found in patients with t(5;12) and del(4q12). The DNA hypomethylating agents azacitidine and decitabine have also been used in treating MDS without a known molecular target and have some effect.

Bibliography is available at Expert Consult.
The Acquired Pancytopenias

Bibliography
Guidelines for Pediatric Red Blood Cell Transfusions

<table>
<thead>
<tr>
<th>CHILDREN AND ADOLESCENTS</th>
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</thead>
<tbody>
<tr>
<td>1. Maintain stable status with acute loss of &gt;25% of circulating blood volume</td>
</tr>
<tr>
<td>2. Maintain hemoglobin &gt;7.0 g/dL in the perioperative period</td>
</tr>
<tr>
<td>3. Maintain hemoglobin &gt;12.0 g/dL with severe cardiopulmonary disease</td>
</tr>
<tr>
<td>4. Maintain hemoglobin &gt;12.0 g/dL during extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>5. Maintain hemoglobin &gt;7.0 g/dL and symptomatic chronic anemia</td>
</tr>
<tr>
<td>6. Maintain hemoglobin &gt;7.0 g/dL and narrow failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INFANTS &lt;4 MO OLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maintain hemoglobin &gt;12.0 g/dL and severe pulmonary disease</td>
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<tr>
<td>2. Maintain hemoglobin &gt;12.0 g/dL during extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>3. Maintain hemoglobin &gt;10.0 g/dL and moderate pulmonary disease</td>
</tr>
<tr>
<td>4. Maintain hemoglobin &gt;12.0 g/dL and severe cardiac disease</td>
</tr>
<tr>
<td>5. Maintain hemoglobin &gt;10.0 g/dL preoperatively and during major surgery</td>
</tr>
<tr>
<td>6. Maintain hemoglobin &gt;7.0 g/dL postoperatively</td>
</tr>
<tr>
<td>7. Maintain hemoglobin &gt;7.0 g/dL and symptomatic anemia</td>
</tr>
</tbody>
</table>

*Words in italics must be defined for local transfusion guidelines.

**Table 470-1**

Red blood cells (RBCs) are transfused to increase the oxygen-carrying capacity of the blood, with the goal to increase or maintain satisfactory tissue oxygenation; this goal may not be achieved simply by increasing the blood hemoglobin concentration or hematocrit by an RBC transfusion because tissue oxygenation depends on several additional factors including oxygen off-loading from RBCs, microvascular blood flow, and diffusion of oxygen into tissue cells. Although some attempts have been made to accurately relate posttransfusion blood hemoglobin concentration or hematocrit values to changes in posttransfusion tissue oxygenation (e.g., improvements in the ratio of cerebral versus mesenteric oxygenation patterns assessed by serial near-infrared spectroscopy measurements), decisions to transfuse RBCs per physiologic indications, rather than degree of anemia, remain investigational.

Because neonates, especially extremely low birthweight preterms are not “small” children (i.e., RBC physiology and the pathophysiology of the anemia of prematurity are unique), RBC transfusions for neonates and older children will be considered separately. Guidelines for RBC transfusions in children and adolescents are based on maintaining a specified hemoglobin or hematocrit level considered to be optimal (per the best evidence available) for the clinical condition present at the time of the transfusion. The guidelines are similar to those for adults (Table 470-1). Transfusions may be given more stringently to children, because normal hemoglobin levels are lower in healthy children than in adults and, as is often the case, children do not have the underlying multiorgan, cardiorespiratory, and vascular diseases that develop with aging in adults to suggest a need for RBC transfusions. Thus, children may compensate better for RBC loss than elderly adults and, as is true for patients of all ages, there is increasing enthusiasm for applying conservative practices (i.e., accept lower pretransfusion hematocrit values to “trigger” an RBC transfusion).

In the perioperative period, it is unnecessary for most children to maintain hemoglobin levels of 8 g/dL or greater, a level frequently desired for adults. The desired preoperative hemoglobin level should take into account the estimated blood loss for the surgical procedure planned and the rate of bleeding. There should be a compelling reason to prescribe any postoperative RBC transfusion, such as continued bleeding with hemodynamic instability, because most children (without continued bleeding) can, in a relatively short time, restore their RBC mass with iron therapy. The most important measures in the treatments of acute hemorrhage are to control the hemorrhage and, if blood loss is modest, to restore the circulating blood volume and tissue perfusion with crystalloid or, less often, colloid solutions. If the estimated blood loss is >25% of the circulating blood volume (>15 mL/kg of an estimated 60 mL/kg total estimated blood volume) and the patient’s condition is unstable despite intravenous fluids, RBC transfusions may be indicated; given with plasma transfusions at a 1:1 ratio of RBC:plasma volumes. Details of combined RBC and plasma transfusions, the volume ratio transfused, and considerations for adding platelet transfusions to treat bleeding patients are controversial. Accordingly, each hospital should develop and follow a “massive transfusion” protocol to ensure consistent practices.

In critically ill children with severe cardiac or pulmonary disease requiring assisted ventilation, it is common practice to maintain the hemoglobin level close to the normal range, although the efficacy of this practice has not been well documented. A similar approach is used for children with acute cardiac, pulmonary, or cardiopulmonary disorders managed with extracorporeal membrane oxygenation.

The pretransfusion blood hemoglobin level or hematocrit that should “trigger” a RBC transfusion is controversial (i.e., restrictive or a low pretransfusion level vs. liberal or a high pretransfusion level).
transfusions. In contrast, the decline occurs earlier and is more pronounced in premature infants, in whom the mean hemoglobin levels maintained close to the normal range by RBC transfusions (i.e., liberal guidelines) have poorer outcomes. Studies in critically ill adults demonstrated better outcomes when the hemoglobin level was maintained at 7-9 g/dL versus 10-12 g/dL. Anemic adults with significant cardiac disease did better with hemoglobin levels maintained at 13 g/dL than at 10 g/dL. Similar studies in children admitted to intensive care units found no inferiority when RBC transfusions were given by restrictive guidelines (transfusion threshold of 7 g/dL). It must be remembered that the children studied were in stable clinical status and needed few transfusions. Therefore, results of the trial cannot be automatically extended to all patients admitted to intensive care units, as unstable critically ill children, who were not studied, may need more liberal RBC transfusions.

With chronic anemia, the decision to transfuse RBCs should not be based solely on blood hemoglobin levels, because children compensate well and may be asymptomatic despite low hemoglobin levels. Patients with iron-deficiency anemia are often treated successfully with oral iron alone, even at hemoglobin levels <5 g/dL. Factors other than hemoglobin concentration to be considered in the decision to transfuse RBCs include: (1) the patient's symptoms, signs, and compensatory capacities; (2) the presence of underlying cardiorespiratory, vascular, and central nervous system disease; (3) the cause and anticipated course of the anemia; and (4) alternative therapies, such as recombinant human erythropoietin (EPO) therapy, which is known to reduce the need for RBC transfusions and to improve the overall condition of children with chronic renal insufficiency (see Chapter 535.2). In anemias that are likely to be permanent, it is also important to balance the detrimental effects of the degree of long-standing anemia on growth and development against the potential toxicity associated with repeated transfusions given to maintain the blood hemoglobin concentration at a specified level. RBC transfusions for disorders such as sickle cell anemia and thalassemia are discussed in Chapters 462.1 and 462.9.

For neonates, nearly all aspects of RBC transfusions remain controversial (i.e., the accepted indications for RBC transfusions; restrictive vs. liberal pretransfusion hemoglobin/hematocrit levels; optimal RBC product to be transfused; fresh vs. stored RBC units), and clinical practices vary greatly. Generally, RBCs are given to maintain a hemoglobin value believed to be the most desirable for each neonate's clinical status (see Table 470-1). Restrictive guidelines (i.e., lower pretransfusion hemoglobin/hematocrit levels) have been compared to more liberal transfusion practices, but both short-term and long-term results/outcomes have been inconsistent and controversial, particularly as to neurodevelopmental status, with poorer outcomes seen in both the restrictive and liberal study arms. Accordingly, conventional guidelines are recommended to avoid problems caused by either undertransfusion or overttransfusion, until more definitive data are published (see Table 470-1).

This clinical approach is imprecise, but more physiologic guidelines/indications such as measurement of RBC mass, calculations of oxygen delivery and tissue extraction, imaging of microcirculatory flow, and comparative measures of tissue perfusion (e.g., ratio of cerebral: mesenteric oxygenation patterns), are too cumbersome for day-to-day clinical practice.

During the first few weeks of life, all neonates experience a decline in circulating RBC mass caused both by physiologic factors and, in sick premature infants, by phlebotomy blood losses. In healthy term infants, the nadir hemoglobin value rarely falls to <11 g/dL at an age of 10-12 wk. This benign physiologic anemia of infancy does not require transfusions. In contrast, the decline occurs earlier and is more pronounced in premature infants, in whom the mean hemoglobin concentration falls to approximately 7 g/dL in infants weighing <1 kg at birth, resulting in the anemia of prematurity, for which there often is need for RBC transfusions.

A key reason that the nadir hemoglobin values of premature infants are lower than those of term infants is the former group's relatively diminished plasma EPO level in response to anemia (see Chapters 103.1 and 446). Another factor is the rapid disappearance of EPO from infant plasma (i.e., accelerated metabolism).

Low plasma EPO levels provide a rationale for the possible use of recombinant EPO in the treatment of anemia of prematurity; treatment with EPO and iron effectively stimulate neonatal erythropoiesis. Despite its erythropoietic effect, the efficacy of EPO therapy to substantially diminish the need for RBC transfusions has not been convincingly demonstrated, particularly for sick, extremely premature neonates, and recombinant EPO has not been widely accepted as a treatment for anemia of prematurity (see Chapter 103.1).

Because of the controversies over recombinant EPO therapy, many low birthweight preterm infants need RBC transfusions (see Table 470-1). Although the practice to maintain a very high hemoglobin level (hemoglobin >13 g/dL or hematocrit >40%) was once widely recommended, currently more restrictive guidelines have been suggested. Consistent with the rationale for oxygen delivery in neonates with severe respiratory disease, it seems appropriate to keep the hemoglobin value relatively high in neonates with severe cardiac disease leading to either cyanosis or congestive heart failure, but convincing and consistent data are lacking.

The optimal hemoglobin level for neonates facing major surgery has not been established. However, it seems reasonable to begin surgery in neonates with the hemoglobin level no lower than 10 g/dL (hematocrit >30%) and to maintain that value during major surgery because even modest blood loss will have a relatively large effect on the small blood volume of the neonate; neonates with underlying pulmonary problems have limited ability to compensate for anemia, and the inferior offloading of oxygen because of the diminished interaction between fetal hemoglobin and 2,3-diphosphoglycerate. Postoperatively, a lower pretransfusion hemoglobin value should be followed to "trigger" a transfusion.

Stable neonates do not require RBC transfusion, regardless of their blood hemoglobin levels, unless they exhibit clinical symptoms attributable to anemia. Proponents of RBC transfusions for symptomatic anemia in preterm neonates believe that the low RBC mass contributes to tachypnea, dyspnea, tachycardia, apnea and bradycardia, feeding difficulties, and lethargy, which can be alleviated by transfusion of RBCs. However, anemia is only one of several possible causes of these problems, and RBC transfusions should only be given when clinical benefit seems likely.

The RBC product of choice to transfuse neonates, infants, children, and adolescents is prestorage leukocyte-reduced RBCs suspended in an anticoagulant/preservative storage solution at a hematocrit value of approximately 60% for storage up to 42 days. The usual dose is 10-15 mL/kg, but transfusion volumes vary greatly, depending on clinical circumstances (continued vs. arrested bleeding, hemolysis). For neonates, some prefer a centrifuged RBC concentrate (hematocrit 70-90%). Unless transfusions are being given to treat rapid bleeding, RBCs are infused slowly (over 2-4 hr) at a dose of approximately 15 mL/kg. In this small-volume setting, because of the small quantity of extracelular fluid transfused and the slow rate of infusion, the type of RBC anticoagulant/preservative solution does not pose any risk for premature infants; there are no data to justify separate inventories of different RBC products for neonates and infants (e.g., citrate-phosphate-dextrose or citrate-phosphate-dextrose-adenine) versus older children (e.g., AS-1, AS-3, or AS-5).

The historical practice of transfusing fresh RBCs (<7 days of storage) for the small-volume (15 mL/kg) transfusions commonly given was supplanted several years ago in most centers by reserving a single unit of RBCs for an infant, from which multiple aliquots were obtained for transfusions as needed throughout the 42 days of storage. Concerns about high concentrations of extracellular potassium, loss of 2,3-diphosphoglycerate, altered RBC shape and deformability, and nitric oxide quenching were found not to pose clinically significant problems. Preterm neonates allocated to "fresh RBC" (<7 day storage) transfusions versus "stored RBC" (up to 42 day storage) transfusions,
have no advantage for fresh RBC transfusions in altering either the composite clinical outcome of mortality plus necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, and intraventricular hemorrhage or of the individual disorders.

For children weighing ≥30 kg who are to undergo elective surgery for which RBC transfusions are likely to be needed, autologous RBC transfusions offer an alternative to donor allogeneic RBCs. Preoperative autologous blood collections from the patient occur up to 6 wk before the surgery and require careful considerations for the volume to be drawn, vascular access, and use of EPO and iron to help restore the donated RBCs. Acute normovolemic hemodilution occurs in the preoperative period, in which blood is withdrawn from the patient and replaced with saline, a task often difficult in centers without experience in the process. Salvaged autologous blood is collected from blood loss during the operation but is impractical unless the volume of blood salvaged is fairly large to permit washing and transfusion of a significant number of RBCs. Because of all of these difficulties plus the relative safety of the usual allogeneic blood supply, autologous RBC transfusions are not commonly used in the pediatric setting.

Bibliography is available at Expert Consult.
Bibliography
Guidelines for platelet (PLT) support of children and adolescents with quantitative and qualitative PLT disorders are similar to those for adults (Table 471-1), in whom the risk of life-threatening bleeding after injury or occurring spontaneously can be related somewhat imprecisely, particularly for the occurrence of spontaneous bleeding to the severity of thrombocytopenia.

For children and adolescents with overt bleeding, therapeutic PLT transfusions should be given when the blood PLT count falls below $50 \times 10^9/L$ and repeated as needed to maintain the PLT count $>50 \times 10^9/L$ during bleeding and for 48 hr after bleeding ceases to allow the clot to "stabilize." Similarly, for a major invasive procedure (e.g., surgical procedure), the PLT count should be maintained $>50 \times 10^9/L$ until any bleeding that occurs ceases and the patient is stable. For minor invasive procedures (e.g., lumbar puncture or placing an intravascular catheter) practices vary, but it is reasonable to maintain the PLT count $>25 \times 10^9/L$.

Historical studies of patients with thrombocytopenia resulting from bone marrow failure suggest that the risk of spontaneous bleeding increases when blood PLT levels fall to $<20 \times 10^9/L$ particularly when hemorrhagic risk factors (infection, organ failure, clotting abnormalities, minor skin/mucosal bleeding, mucosal lesions, severe graft-versus-host disease, or anemia) are present. In this high-risk setting, prophylactic PLT transfusions are given to maintain a PLT count $>20 \times 10^9/L$. This threshold has been challenged by several studies of adult patients, who, in many instances, were carefully selected to be in relatively good clinical condition without hemorrhagic risk factors. Consequently, a higher PLT transfusion trigger of $50 \times 10^9/L$ is recommended for stable (i.e., low-risk) patients.

In practice, severe thrombocytopenia that is prolonged beyond 1 wk commonly becomes complicated by the development of risk factors including fever, antimicrobial therapy, graft-versus-host disease, active bleeding, need for an invasive procedure, disseminated intravascular coagulation, and liver or kidney dysfunction with clotting abnormalities. In these situations, prophylactic PLT transfusions are given to maintain relatively high PLT counts (e.g., at least $>30 \times 10^9/L$). Despite the desire by some physicians to elevate the blood PLT count to $80 \times 10^9/L$ or $100 \times 10^9/L$, there are no definitive data to justify a true benefit of PLT transfusions given at a PLT count $>50 \times 10^9/L$, unless bleeding is ongoing with a PLT count between 50 and $100 \times 10^9/L$ and thrombocytopenia seems to be the only cause for the bleeding.

Qualitative PLT disorders may be inherited or acquired (in advanced hepatic or renal insufficiency or when blood flows through an extracorporeal circuit, such as during extracorporeal membrane oxygenation or cardiopulmonary bypass). In patients with inherited disorders, PLT transfusions are justified only if the risk of significant bleeding is quite high or if bleeding is overt because inherited PLT dysfunction often is lifelong and repeated transfusions may lead to alloimmunization and refractoriness (i.e., poor response to PLT transfusions). Accordingly, prophylactic PLT transfusions are rarely justified, unless an invasive procedure is planned, and therapeutic PLT transfusions must be given judiciously.

When managing patients with PLT dysfunction, it is important to remember that, an abnormal test result with a modern PLT function device or, historically, a bleeding time more than twice the upper limit of normal provides diagnostic evidence of PLT dysfunction. However, an abnormal bleeding time or any other abnormal laboratory test is poorly predictive of hemorrhagic risk and/or the need to transfuse PLTs. Alternative therapies, particularly desmopressin acetate, should be considered to avoid PLT transfusions. Antiplatelet medications (nonsteroidal antiinflammatory drugs) should also be avoided.

In neonates, thrombopoiesis and the risks of bleeding are substantially different from that in older children; the approach to thrombocytopenia and PLT transfusions likewise differs (see Table 471-1). Thrombopoietin (TPO) levels are higher in healthy neonates than in older individuals. Megakaryocyte progenitors of neonates are more sensitive to TPO, have higher proliferative potential, and give rise to larger megakaryocyte colonies than do adult PLT progenitors. Fetal/neonatal megakaryocytes are smaller in size and have lower ploidy than do their adult counterparts; this is an important factor because small megakaryocytes of low ploidy produce fewer PLTs than larger megakaryocytes of higher ploidy. Presumably, this allows the expanding marrow of the growing fetus and neonate to be supplied with sufficient numbers of megakaryocytes, yet not allowing blood PLT counts to become excessively high during proliferation, because of the lower numbers of PLTs produced by each megakaryocyte.

An important contrasting point is that older children and adults respond to situations of increased demand for PLTs by first increasing megakaryocyte size and ploidy, which is followed in 3–5 days by

**Table 471-1 Guidelines for Pediatric Platelet Transfusion**

**CHILDREN AND ADOLESCENTS**

1. Maintain PLT count $>50 \times 10^9/L$ with bleeding
2. Maintain PLT count $>50 \times 10^9/L$ with major invasive procedure; $>25 \times 10^9/L$ with minor
3. Maintain PLT count $>20 \times 10^9/L$ and marrow failure WITH hemorrhagic risk factors
4. Maintain PLT count $>10 \times 10^9/L$ and marrow failure WITHOUT hemorrhagic risk factors
5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding or invasive procedure

**INFANTS ≤4 MO OLD**

1. Maintain PLT count $>100 \times 10^9/L$ with bleeding or during extracorporeal membrane oxygenation
2. Maintain PLT count $>50 \times 10^9/L$ and an invasive procedure
3. Maintain PLT count $>20 \times 10^9/L$ and clinically stable
4. Maintain PLT count $>50 \times 10^9/L$ and clinically unstable and/or bleeding or not when on indomethacin, nitric oxide, antibiotics, etc. affecting PLT function
5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding invasive procedure

*Words in italics must be defined for local transfusion guidelines.

PLT, platelet.
increased megakaryocyte number. In thrombocytopenic neonates, megakaryocyte numbers increase, but not their size. Moreover, although cytoplasmic maturation is achieved per TPO stimulation, increases in ploidy are relatively diminished and actually appear to be inhibited by TPO, resulting in large numbers of small megakaryocytes that are cytoplasmically mature, but with low ploidy and, consequently, lower PLT production.

Blood PLT counts ≥150 × 10^9/L are present after 17 wk gestational age, and it is accepted that neonates have blood PLT counts in the same range as older children and adults (150,000-450,000/µL). However, recent data suggest a lower limit of 120,000/µL for extremely small preterm infants. Approximately 1% of term infants demonstrate PLT counts <150 × 10^9/L, but bleeding in such infants is rare. In contrast, 25-35% of preterm infants treated in intensive care units exhibit blood PLT counts <150 × 10^9/L at some time during admission, with approximately 4% overall receiving PLT transfusions. Notably, when only extremely low birthweight preterm infants (<1 kg birthweight) were considered in one report, 73% had PLT counts <150 × 10^9/L and 62% of thrombocytopenic neonates received PLT transfusions. Multiple pathogenetic mechanisms underlie thrombocytopenia in these sick neonates; predominantly accelerated PLT destruction plus diminished PLT production, as evidenced by decreased numbers of megakaryocyte progenitors and relatively low upregulation of TPO levels during thrombocytopenia, compared with thrombocytopenic children and adults.

Blood PLT counts <100 × 10^9/L pose significant clinical risks for premature neonates. Bleeding time may be prolonged at PLT counts <100 × 10^9/L in infants with a birthweight <1.5 kg, and PLT dysfunction is suggested by bleeding times (a test no longer performed) that are disproportionately long for the degree of thrombocytopenia. The risk of hemorrhage may be increased in thrombocytopenic infants. However, in a randomized trial, transfusing PLTs prophylactically whenever the PLT count fell to <150 × 10^9/L (i.e., at the lower limit of the normal range) to maintain the average PLT count at >200 × 10^9/L, compared to not transfusing PLTs until the PLT count fell to <50 × 10^9/L to maintain the average PLT count at approximately 100 × 10^9/L, did not result in a lower incidence of intracranial hemorrhage (28% vs. 26%, respectively). Thus, there is no documented benefit for prophylactic PLT transfusions to maintain PLT counts within the normal range or to correct modest thrombocytopenia (PLT count >50 × 10^9/L). As an exception, infants with inherited PLT dysfunction disorders and bleeding, and those at high risk of bleeding owing to acquired PLT dysfunction, such as during extracorporeal membrane oxygenation, commonly receive transfusions to keep their PLT counts >100 × 10^9/L.

Table 471-1 lists guidelines that are acceptable to many neonatologists. One particularly contentious issue is how to manage critically ill neonates receiving drugs/agents known to adversely affect PLT function (e.g., indomethacin, nitric oxide, antibiotics). Some reports suggest increased risk of bleeding for these neonates, but the efficacy of PLT transfusions has not been convincingly proven, particularly when given prophylactically. For optimal PLT transfusion practices, each hospital should modify the guidelines to comply with local practices, and audits/reviews should be performed to avoid violations of the recommended practices. The posttransfusion goal of most PLT transfusions is to raise the PLT count well above 50 × 10^9/L, hopefully to ≥100 × 10^9/L. These increases can be achieved consistently in children weighing up to 30 kg by infusion of 5-10 mL/kg of standard (unmodified) PLT concentrates, obtained either from processing whole blood units or by plateletpheresis. For larger children, the appropriate dose is 3-4 pooled whole blood–derived PLT units or 1 apheresis unit. Because PLT concentration/quantity varies in different PLT products made available for transfusion, each hospital should monitor posttransfusion PLT counts to determine the dose that works best locally. PLT concentrates should be transfused as rapidly as the patient’s overall condition permits, certainly within 2 hr. Neonates/infants requiring repeated PLT transfusions should receive leukocyte-reduced blood products, including PLT concentrates, to diminish alloimmunization and PLT refractoriness and to reduce the risk of transfusion-transmitted cytomegalovirus infection.

Routinely reducing the volume of PLT concentrates for infants and small children by additional centrifugation steps is both unnecessary and unwise. Transfusion of 10 mL/kg of an unmodified PLT concentrate is adequate because it adds approximately 10 × 10^9 PLTs to 70 mL of blood (the estimated intravascular blood volume of a 1 kg neonate), a dose/volume calculated to increase the PLT count by 100 × 10^9/L. This calculated increment is consistent with actual posttransfusion increment reported in patients. Moreover, 10 mL/kg is not an excessive transfusion volume, provided that the intake of other IV fluids, medications, and nutrients is monitored and adjusted.

It is important to select PLT units for transfusion with the donor ABO group identical to that of the neonate/infant and to avoid repeated transfusion of group O PLTs to group A or B recipients because passive transfusion anti-A or anti-B in group O plasma, can occasionally lead to hemolysis.

Bibliography is available at Expert Consult.
Bibliography

Chapter 472  Neutrophil (Granulocyte) Transfusions
Ronald G. Strauss

Table 472-1 lists guidelines for granulocyte transfusion (GTX). GTX has been used sparingly in older infants and children. The current ability to collect markedly higher numbers of neutrophils from donors stimulated with combined recombinant granulocyte colony-stimulating factor (G-CSF) plus dexamethasone has led to renewed interest for patients with neutropenic infections, particularly when severe neutropenia is prolonged (e.g., in the setting of placental/cord blood hematopoietic progenitor cell transplantation). Because of the higher neutrophil yields with this collection approach, adding GTX to antibiotics should be considered at institutions where neutropenic patients continue either to die of progressive bacterial and fungal infections or to suffer substantial morbidity despite optimal antiinfection measures, including antibiotics and recombinant myeloid growth factors.

The use of GTX added to antibiotics for children with severe neutropenia (blood neutrophil count <0.5 × 10^9/L) because of bone marrow failure is similar to that for adults. Unfortunately, two randomized clinical trials comparing antibiotics plus GTX from donors stimulated with G-CSF plus dexamethasone versus antibiotics without GTX

Table 472-1  Guidelines for Pediatric Granulocyte Transfusions*

<table>
<thead>
<tr>
<th>CHILDREN AND ADOLESCENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe neutropenia (blood neutrophil count &lt;0.5 × 10^9/L) and infection (bacterial, yeast, or fungal) unresponsive or progressive despite appropriate antimicrobial therapy</td>
</tr>
<tr>
<td>2. Qualitative neutrophil defect, neutropenia not required, and infection (bacterial or fungal) unresponsive or progressive to appropriate antimicrobial therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INFANTS ≤4 MO OLD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood neutrophil count &lt;3.0 × 10^9/L in 1st wk of life or &lt;1.0 × 10^9/L thereafter and fulminant bacterial infection.</td>
</tr>
</tbody>
</table>

*Words in italics must be defined for local transfusion guidelines.
†No longer commonly used.
to treat neutropenic infections in children have not provided definitive guidelines. However in practice, neutropenic patients with bacterial infections usually show response to antibiotics alone, provided bone marrow function recovers within the 1st 7-10 days of infection onset so that severe neutropenia is relatively brief. Children with newly diagnosed acute lymphoblastic leukemia show rapid response to induction chemotherapy, and they rarely are candidates for GTX. In contrast, infected children with more sustained bone marrow failure and consequent severe neutropenia (e.g., acute myeloblastic leukemia, malignant neoplasms resistant to treatment, severe aplastic anemia, and placental/cord blood hematopoietic progenitor cell transplant recipients) may benefit when GTX is added to antibiotics.

Currently, the efficacy of GTX obtained from G-CSF plus dexamethasone-stimulated donors for bacterial sepsis unresponsive to antibiotics in patients with severe neutropenia (blood neutrophil count <0.5 × 10^9/L) is not well supported by trials in children. In contrast, GTX efficacy for yeast and fungal infections remains unproven despite transfusing GTX with relatively large numbers of neutrophils.

Children with qualitative neutrophil defects (neutrophil dysfunction) usually have adequate or even increased numbers of blood neutrophils but suffer serious infections, because their neutrophils kill pathogenic microorganisms inefficiently. Neutrophil dysfunction syndromes are rare; accordingly, no definitive studies have established GTX efficacy. However, several patients with progressive life-threatening infections have shown striking improvement with the addition of GTX, often given for long periods of time, to antimicrobial therapy. These disorders are chronic, and because of the risk of inducing alloimmunization to leukocyte antigens, and in some patients with chronic granulomatous disease, to antigens of the Kell system of red blood cells, GTX is recommended only when serious infections are clearly unresponsive to antimicrobial drugs.

Neonates are unusually susceptible to severe bacterial infections, and a number of defects of neonatal body defenses contribute, including actual or “relative” neutropenia. Neonates with fulminant sepsis who exhibit relative neutropenia (blood neutrophil count <3.0 × 10^9/L during the 1st wk of life and <1.0 × 10^9/L thereafter) and a severely diminished neutrophil marrow storage pool (with <10% of nucleated marrow cells being postmitotic neutrophils) are at risk of dying if treated only with antibiotics. GTX is rarely used because results of clinical trials are mixed and not uniformly convincing, and it is difficult to obtain neutrophil apheresis concentrates in timely fashion.

Current data are insufficient to determine whether recombinant myeloid growth factors have a role in treating septic neonates, despite the fact that both G-CSF and granulocyte-macrophage colony-stimulating factor have been demonstrated to enhance myelopoiesis and raise neutrophil counts in infants. Importantly, G-CSF is efficacious for the long-term treatment of several types of severe congenital neutropenia.

If the decision to provide a GTX has been made, an adequate dose of neutrophils/granulocytes collected by leukapheresis must be transfused as shortly after collection as possible. To facilitate this, experienced donors with required infectious disease (HIV, hepatitis) tests having been done recently (usually within the past 30 days) are selected, and the collected neutrophils are transfused before results of current infectious disease tests are known (i.e., infectious disease test results are “waived”).

Neonates and infants weighing <10 kg should receive 1-2 × 10^9/kg neutrophils per each GTX. Larger infants and small children should receive a minimal total dose of 1 × 10^10 neutrophils per each GTX. The preferred dose for adolescents is 5-8 × 10^10 neutrophils per each GTX, a dose requiring donors to be stimulated with G-CSF plus dexamethasone. GTX should be given daily until either the infection resolves or the blood neutrophil count is sustained above 1.5 × 10^9/L for a few days. Because neutrophils transfused per the GTX often passively increase the blood neutrophil count, it may be necessary to skip 1-2 days of GTXs to be certain severe neutropenia does not recur, as would be seen if endogenous myelopoiesis had not recovered.

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


Guidelines for plasma transfusion in pediatric patients (Table 473-1) are similar to those for adults but with the understanding that plasma levels of coagulant and anticoagulant proteins can be developmentally quite low in preterm infants so that transfusions of plasma and plasma-derived commercial concentrates should be determined by actual bleeding or a significant risk of bleeding, not simply prolonged clotting time results. Plasma is transfused to replace clinically significant deficiencies of plasma proteins for which more highly purified protein concentrates that have been treated to reduce infectious disease risks are not available nearly always to provide clotting proteins when bleeding is occurring or in settings when prevention of bleeding is deemed critical.

Two interchangeable plasma products are available for transfusion, plasma frozen within 8 hr of collection (fresh-frozen plasma) and plasma frozen within 24 hr of collection. Although levels of factors V and VIII are modestly reduced in the latter plasma product (generally, not more than 25% lower), they are equally efficacious for all indications for which plasma is transfused (see Table 473-1). Recommendations for the volume of plasma to be transfused vary with the specific protein being replaced and the severity of the deficiency, but a starting dose of 15 mL/kg is usually sufficient to elevate plasma levels satisfactorily.

Transfusion of plasma is efficacious for the treatment of deficiencies of clotting factors II, V, X, and XI. Deficiencies of factor XIII and fibrinogen are treated either with cryoprecipitate or specific commercial concentrates; although for patients being given large doses of plasma (e.g., in massive transfusion settings or to treat bleeding in liver failure), additional sources of fibrinogen may not be necessary, as plasma contains large amounts of fibrinogen. It is always useful to include a measurement of plasma fibrinogen when performing clotting assays (e.g., prothrombin time [PT]/international normalized ratio [INR] and activated partial thromboplastin time [aPTT]).

Transfusion of plasma is not recommended for the treatment of patients with severe hemophilia A or B, von Willebrand disease, or factor VII deficiency, because safer factors VII, VIII, IX, and von Willebrand factor concentrates are available. Moreover, mild to moderate hemophilia A and certain types of von Willebrand disease can be treated with intranasal or intravenous desmopressin (see Chapter 477).

<table>
<thead>
<tr>
<th>Table 473-1</th>
<th>Guidelines for Pediatric Plasma Transfusions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe clotting factor deficiency AND bleeding</td>
<td></td>
</tr>
<tr>
<td>2. Severe clotting factor deficiency AND an invasive procedure</td>
<td></td>
</tr>
<tr>
<td>3. Emergency reversal of warfarin effects</td>
<td></td>
</tr>
<tr>
<td>4. Dilutional coagulopathy and bleeding (e.g., massive transfusion)</td>
<td></td>
</tr>
<tr>
<td>5. Anticoagulant protein (antithrombin III, proteins C and S) replacement</td>
<td></td>
</tr>
<tr>
<td>6. Plasma exchange replacement fluid for thrombotic thrombocytopenic purpura or for disorders with overt bleeding or in which there is risk of bleeding because of clotting protein abnormalities (e.g., liver failure)</td>
<td></td>
</tr>
</tbody>
</table>

*Words in italics must be defined for local transfusion guidelines.
functional deficiencies of factors II, VII, IX, and X cannot be rapidly reversed by vitamin K). Prothrombin "complex" concentrates can also be used for this purpose.

Results of screening coagulation tests (PT/INR, aPTT, and thrombin times, and plasma fibrinogen levels) should not be assumed by themselves to reflect the integrity of the coagulation system or be regarded as indications for plasma transfusions. This is particularly true for neonates. To justify plasma transfusions, coagulation test results must be related to the patient's clinical condition pertaining to bleeding and/or the risk of bleeding. Transfusion of plasma in patients with chronic liver disease and prolonged clotting times is not recommended unless bleeding is present or an invasive procedure is planned, because correction of the clotting factor deficiencies is brief and of questionable benefit.

Plasma also contains several anticoagulant proteins (antithrombin III, protein C, and protein S) whose deficiencies have been associated with thrombosis. In selected situations, plasma may be appropriate as replacement therapy, along with anticoagulant treatment, in patients with these disorders; when available, purified concentrates are preferred. Other indications for plasma include replacement fluid during plasma exchange in patients with thrombotic thrombocytopenic purpura (i.e., thrombotic microangiopathies) or other disorders for which plasma is likely to be beneficial (plasma exchange in a patient with overt bleeding due to the underlying disorder such as Goodpasture syndrome or vasculitis or disorders with significant severe coagulopathy that would be made substantially more severe by replacement using albumin solutions only). Plasma is not indicated for correction of hypovolemia or as immunoglobulin replacement therapy, because safer alternatives exist (albumin or crystalloid solutions and IV immunoglobulin, respectively).

In neonates, clotting times are "physiologically" prolonged owing to developmental deficiency of clotting proteins; plasma should be transfused only after reference to normal values adjusted for the birthweight and age of the infant (i.e., not to normal ranges for older children and adults). The indications for plasma in neonates include: (1) reconstitution of red blood cell (RBC) concentrates to simulate whole blood for use in massive transfusions (exchange transfusion, cardiac bypass surgery, and extracorporeal membrane oxygenation); (2) hemorrhage secondary to vitamin K deficiency; (3) disseminated intravascular coagulation with bleeding; and (4) bleeding in congenital coagulation factor deficiency when more specific treatment is either unavailable or inappropriate. The use of prophylactic plasma transfusion to prevent intraventricular hemorrhage in premature infants is not recommended. Plasma should not be used as a suspending agent to adjust the hematocrit values of RBC concentrates before small-volume RBC transfusions to neonates because it offers no apparent medical benefit over the use of sterile solutions such as crystalloid and albumin. Similarly, the use of plasma in partial exchange transfusion for the treatment of neonatal hyperviscosity syndrome is unnecessary, because safer crystalloid or colloid solutions are available.

In the treatment of bleeding infants, cryoprecipitate is often considered because of its small infusion volume. However, cryoprecipitate contains significant quantities of only fibrinogen, von Willebrand factor, and factors VIII and XIII. Thus, it is not effective for treating the usual clinical situation in bleeding infants in which multiple clotting factor deficiencies exist.

In preliminary studies, infusions of very small volumes of recombinant activated factor VII have been lifesaving in patients with hemorrhage caused by several mechanisms. Because the efficacy and toxicity of factor VIIa have not been fully defined in these "off-label" uses (not approved by the U.S. Food and Drug Administration), it must be considered experimental therapy at this time.

*Bibliography is available at Expert Consult.*
Bibliography


The greatest risk of a blood transfusion is receiving a transfusion intended for another patient; misidentification usually as a result of mistakes made labeling the patient's blood sample sent to the blood bank or not accurately matching the unit with the patient at the time the blood is transfused. This risk is particularly high for infants because identification bands may not be attached directly to their bodies, difficulties in drawing blood samples for pretransfusion compatibility testing may lead to deviations from usual policies, and infants cannot speak to identify themselves. Thus, particular care must be taken to ensure accurate patient and blood sample identification.

Although the infectious disease risks of allogeneic blood transfusions are extremely low, transfusions must be given judiciously because "emerging infections" are a constant threat, and testing is not done for every microorganism possibly transmitted by blood transfusions (Table 474-1, Fig. 474-1). Taking nucleic acid amplification testing

<table>
<thead>
<tr>
<th>ADVERSE EFFECT</th>
<th>ESTIMATED RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile reaction</td>
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<tr>
<td>Urticaria or other cutaneous reaction</td>
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<tr>
<td>Red blood cell alloimmunization</td>
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<td>Mistransfusion</td>
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<td>Fatal hemolysis</td>
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<td>Transfusion-related acute lung injury (TRALI)</td>
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<td>Malaria</td>
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<td>Variant Creutzfeldt-Jakob prion disease</td>
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</table>

Part XXI

Transfusion-associated cytomegalovirus (CMV) has been nearly eliminated by transfusion of leukocyte-reduced cellular blood products or by selection of blood collected from donors who are seronegative for antibody to CMV. Although it is logical to hypothesize that first collecting blood components from CMV-seronegative donors and then removing the white blood cells might further improve safety, no data are available to document the superior efficacy of this combined approach. Importantly, considerable care must be taken not to place children at risk of delayed or missed transfusions while awaiting/searching for blood from CMV-seronegative donors to, then, leukocyte-reduce (i.e., risks must not be taken for practices with no established benefits).

Another consideration is that emerging data suggest that this combined approach using CMV-seronegative blood, surprisingly, may be incorrect. Large quantities of CMV viral material are present “free” in the plasma of healthy-appearing donors during the early phase of primary infection (while CMV antibodies are either absent “[window” phase] or are newly emerging and are at low inconsistently detected levels in plasma), rather than being leukocyte-associated as occurs with CMV as substantial quantities of immunoglobulin G antibodies appear. As a result of this biology of CMV primary infection, plasma “free” virus will not be removed by leukocyte-reduction during early infection, and CMV-seronegative donors who may be asymptomatic or deny symptoms of infection during blood donor screening will be misclassified as being CMV safe. They are not safe because antibody is below the limits of detection, while plasma “free” CMV is plentiful during early infection. Because nearly all plasma “free” CMV disappears and becomes almost exclusively cell-associated, once donors are CMV-seropositive with antibody present for several months, it has been proposed that the best method to reduce CMV risk may be to effectively perform leukocyte reduction of blood from donors known to be CMV-seropositive for at least 1 year. However, data to prove the efficacy of this proposal are lacking, and in practice, several studies have shown that the most efficacious method currently available to prevent transfusion-transmitted CMV is to perform leukocyte-reduction in the blood center/bank without regard for the CMV-antibody status of the donor/unit (i.e., leukocyte-reduction alone performed by the blood center/bank is sufficient).

Additional infectious risks include other types of hepatitis (A, B, E) and retroviruses (human T-cell lymphotropic virus types I and II, and HIV-2), syphilis, parvovirus B19, Epstein-Barr virus, human herpesvirus 8, West Nile virus, yellow fever vaccine virus, malaria, babesiosis, Anaplasmaphagocytophilum, and Chagas disease. Variant Creutzfeldt-Jacob disease has also been transmitted by blood transfusions in humans. All are reported very uncommonly, but nonetheless, provide the rationale to transfuse only when true benefits are likely.

Transfusion-associated risks of a noninfectious nature that may occur include hemolytic and nonhemolytic transfusion reactions, fluid overload, graft versus host disease, electrolyte and acid-base imbalances, iron overload if repeated transfusions are needed long term, increased susceptibility to oxidant damage, exposure to plasticizers, hemolysis with T-antigen activation of red blood cells, posttransfusion purpura, transfusion-related acute lung injury, post-transfusion immunosuppression and immunomodulation, and alloimmunization (see Table 474-1). The risk of transfusion-related acute lung injury may be reduced by reducing the use of plasma or platelets from female donors who were possibly sensitized during pregnancy or are negative for human leukocyte antigen (HLA) antibodies.

Immunologic adverse effects, including immunosuppression, immunomodulation, and alloimmunization may be reduced by leukocyte-reduction. Transfusion reactions and alloimmunization to red blood cell and leukocyte antigens seem to be uncommon in infants, perhaps because of developmental immaturity of the immune system or deficient cytokine production. When they do occur, adverse effects are seen primarily in massive transfusion settings, such as exchange

Figure 474-1 Risks of major transfusion-transmitted viruses related to interventions, and accelerating rate of emerging infectious diseases of concern to blood safety. Evolution of the risks of transmission by blood transfusion for HIV, hepatitis B virus, and hepatitis C virus. Major interventions to reduce risks are shown below the time line on the x axis. Emerging infectious disease threats in the past 20 yr are shown above in the top right quadrant of the figure. Ab, antibody; Ag, antigen; CHIKV, chikungunya virus; DENV, dengue virus; HBSAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICL, idiopathic CD4 T-lymphocytopenia; NANB, non-A, non-B hepatitis; NAT, nucleic acid testing; PTLVs, primate T-lymphotropic viruses; SARS, severe acute respiratory syndrome; SFV, simian foamy virus; vCJD, variant Creutzfeldt-Jakob disease; WNV, West Nile virus; XMRV, xenotropic murine leukemia virus-related virus. (From Busch MP. Transfusion-transmitted viral infections: building bridges to transfusion medicine to reduce risks and understand epidemiology and pathogenesis. 2005 Emily Cooley Award Lecture, Transfusion 46:1624-1640, 2006.)
transfusions and trauma or surgery, in which relatively large quantities of blood are needed but are rare with the small-volume transfusions usually given.

Premature infants are known to have immune dysfunction, but their relative risk of posttransfusion graft-versus-host disease is controversial. The postnatal age of the infant, the number of immunocompetent lymphocytes in the transfusion product, the degree of HLA compatibility between donor and recipient, and other poorly described phenomena determine which infants are truly at risk for graft-versus-host disease. Regardless, many centers caring for preterm infants transfuse exclusively irradiated cellular products. Directed donations with blood drawn from blood relatives must always be irradiated because of the risk of engraftment with transfused HLA-homozygous, haploidentical lymphocytes. Cellular blood products given as intrauterine and/or exchange transfusions should be irradiated, as are transfusions for patients with severe congenital immunodeficiency disorders (severe combined immunodeficiency syndrome and DiGeorge syndrome requiring heart surgery) and transfusions for recipients of hematopoietic progenitor cell transplants. Other groups who are potentially at risk but for whom no conclusive data are available include patients given T-cell antibody therapy (antithymocyte globulin or OKT3), those with organ allografts, those receiving immunosuppressive drug regimens, and those infected with HIV.

Current practice uses irradiation from a cesium, cobalt, or linear acceleration source at doses ranging from 2,500-5,000 cGy; a minimum dose of 2,500 cGy is required. All cellular blood components should be irradiated, but frozen “acellular” products, such as plasma and cryoprecipitate, do not require it. Leukocyte reduction cannot be substituted for irradiation to prevent graft versus host disease.

Bibliography is available at Expert Consult.
Chapter 474  ●  Risks of Blood Transfusions  2379.e1

Bibliography
Hemostasis is the active process that clots blood in areas of blood vessel injury yet simultaneously limits the clot size only to the areas of injury. Over time, the clot is lysed by the fibrinolytic system, and normal blood flow is restored. If clotting is impaired, hemorrhage occurs. If clotting is excessive, thrombotic complications ensue. The hemostatic response needs to be rapid and regulated such that trauma does not trigger a systemic reaction but must initiate a rapid, localized response. Key to the speed and coordination of response is that when a platelet adheres to a site of vascular injury, the platelet surface provides a reaction surface where clotting factors bind. The active enzyme is brought together with its substrate and a catalytic cofactor on a reaction surface, accelerating reaction rates and providing activated products for reaction with clotting factors further down the coagulation cascade. Active clotting is controlled by negative feedback loops that inhibit the clotting process when the procoagulant process comes in contact with intact endothelium. The main components of the hemostatic process are the vessel wall, platelets, coagulation proteins, anticoagulant proteins, and fibrinolytic system. Most components of hemostasis are multifunctional; fibrinogen serves as the ligand between platelets during platelet aggregation and also serves as the substrate for thrombin that forms the fibrin clot. Platelets provide the reaction surface on which clotting reactions occur, form the plug at the site of vessel injury, and contract to constrict and limit clot size.

THE PROCESS

The intact vascular endothelium is the primary barrier against hemorrhage. The endothelial cells that line the vessel wall normally inhibit coagulation and provide a smooth surface that permits rapid blood flow.

After vascular injury, vasoconstriction occurs and flowing blood comes in contact with the subendothelial matrix (Fig. 475-1). In flowing blood, when exposed to subendothelial matrix proteins, von Willebrand factor (VWF) changes conformation and provides the glue to which the platelet VWF receptor, the glycoprotein Ib complex, binds, tethering platelets to sites of injury. When the VWF receptor binds its ligand, complex signaling occurs from the outside membrane receptor to intracellular pathways, activating the platelets and triggering secretion of storage granules containing adenosine diphosphate (ADP), serotonin, and stored plasma and platelet membrane proteins. Upon activation, the platelet receptor for fibrinogen, $\alpha_{IIb} \beta_3$, is switched on (“inside out” signaling) to bind fibrinogen and triggers the aggregation and recruitment of other platelets to form the platelet plug. Multiple physiologic agonists can trigger platelet activation and aggregation, including ADP, collagen, thrombin, and arachidonic acid. Aggregation involves the interaction of specific receptors on the platelet surface with plasma hemostatic proteins, primarily fibrinogen.

One of the subendothelial matrix proteins that are exposed after vascular injury is tissue factor. Just as exposed subendothelial matrix proteins bind VWF, exposed tissue factor binds to factor VII and

Figure 475-1 The clotting cascade, with sequential activation and amplification of clot formation. Many of the factors (F) are activated by the clotting factors shown above them in the cascade. The activated factors are designated by the addition of an a. On the right side, the major anticoagulants and the sites that they regulate are shown: Tissue factor pathway inhibitor (TFPI) regulates tissue factor (TF); factor VIIa, protein C, and protein S (P-C/S) regulate factors VIII and V; and anti-thrombin III (AT-III) regulates factor Xa and thrombin (factor IIa). The dotted line shows that, in vivo, TF and factor VIIa activate both factors IX and X, but that, in vitro, only the activation of factor X is measured. Unactivated factor VIII, when bound to its carrier protein, von Willebrand factor, is protected from protein C inactivation. When thrombin, or factor Xa activates factor VIII, it becomes unbound from von Willebrand factor, whereupon it can participate with factor IXa in the activation of factor X in the presence of phospholipid (PL) and Ca$^{2+}$ (the “tenase” complex). Factor XIIa crosslinks the fibrin clot and thereby makes it more stable. Prekallikrein, high-molecular-weight kininogen (HMWK), and factor XII are shown in blue because they do not have a physiologic role in coagulation, although they contribute to the clotting time in partial thromboplastin time (PTT).
activates the clotting cascade, as shown in Figure 475-2. The activated clotting factor then initiates the activation of the next sequential clotting factor in a systematic manner. Our understanding of the sequence of steps in the cascade followed assignment of the numerals for the clotting factors for the participant proteins, and thus the sequence seems "out of numerical order." During the process of platelet activation, internalized platelet phospholipids (primarily phosphatidylserine) become externalized and interact at 2 specific, rate-limiting steps in the clotting process—those involving the cofactors factor VIII (X-ase complex) and factor V (prothrombinase complex). Both of these reactions are localized to the platelet surface and bring together the active enzyme, an activated cofactor, and the zymogen that will form the next active enzyme in the cascade. This sequence results in amplification of the process, which supplies a burst of clotting where it is physiologically needed. In vivo, autocatalysis of factor VII generates small amounts of VIIa continuously, so the system is always poised to act. Near the bottom of the cascade, the multipotent enzyme thrombin is formed. Thrombin converts fibrinogen into fibrin, activates factors V, VIII, and XI, and aggregates platelets. Activation of factor XI by thrombin amplifies further thrombin generation and contributes to inhibition of fibrinolysis. Thrombin also activates factor XIII. The stable fibrin-platelet plug is ultimately formed through clot retraction and cross linking of the fibrin clot by factor XIIIa.

Virtually all procoagulant proteins are balanced by an anticoagulant protein that regulates or inhibits procoagulant function. Four clinically important, naturally occurring anticoagulants regulate the extension of the clotting process: antithrombin III (AT-III), protein C, protein S, and tissue factor pathway inhibitor. AT-III is a serine protease inhibitor that regulates factor Xa and thrombin primarily and factors IXa, XIa, and XIIa to a lesser extent. When thrombin in flowing blood encounters intact endothelium, thrombin binds to thrombomodulin, its endothelial receptor. The thrombin–thrombomodulin complex then converts protein C into activated protein C. In the presence of the cofactor protein S, activated protein C proteolyses and inactivates factor Va and factor VIIIa. Inactivated factor Va is, in fact, a functional anticoagulant that inhibits clotting. Tissue factor pathway inhibitor limits activation of factor X by factor VIIa and tissue factor and shifts the activation site of tissue factor and factor VIIa to that of factor IX (see Figs. 475-1 and 475-2).

Once a stable fibrin-platelet plug is formed, the fibrinolytic system limits its extension and also lysed the clot (fibrinolysis) to reestablish vascular integrity. Plasmin, generated from plasminogen by either urokinase-like or tissue-type plasminogen activator, degrades the fibrin clot. In the process of dissolving the fibrin clot, fibrin degradation products are produced. The fibrinolytic pathway is regulated by plasminogen activator inhibitors and α2-antiplasmin, as well as by the thrombin-activatable fibrinolytic inhibitor. Finally, the flow of blood in and around the clot is crucial, because flowing blood returns to the liver, where activated clotting factor complexes are removed and new procoagulant and anticoagulant proteins are synthesized to maintain homeostasis of the hemostatic system.

**PATHOLOGY**

Congenital deficiency of an individual procoagulant protein leads to a bleeding disorder, whereas deficiency of an anticoagulant (clotting factor inhibitor) predisposes the patient to thrombosis. In acquired hemostatic disorders, there are frequently multiple problems with homeostasis that perturb and dysregulate hemostasis. A primary illness (sepsis) and its secondary effects (shock and acidosis) activate coagulation and fibrinolysis and impair the host’s ability to restore normal hemostatic function. When sepsis triggers disseminated intravascular coagulation, platelets, procoagulant clotting factors, and anticoagulant proteins are consumed, leaving the hemostatic system unbalanced and prone to bleeding or clotting. Similarly, newborn infants and patients with severe liver disease have synthetic deficiencies of both procoagulant and anticoagulant proteins. Such dysregulation causes the patient to be predisposed to both hemorrhage and thrombosis with mild or moderate triggers that result in major alterations in the hemostatic process.

In the laboratory evaluation of hemostasis, parameters are manipulated to allow assessment of isolated aspects of hemostasis and limit the multifunctionality of some of its components. The coagulation
process is studied in plasma anticoagulated with citrate to bind calcium, with added phospholipid to mimic the reaction surface normally provided by the platelet membrane and with a stimulus to trigger clotting. Calcium is added to restart the clotting process. This results in anomalies such that the in vivo physiologic pathway of clotting in which factor VIIa activates factor IX is bypassed; instead, in prothrombin time (PT), factor VIIa activates factor X. If these were truly the physiologic situation, then there would be an in vivo bypass mechanism that would ameliorate severe factor VIII and factor IX deficiencies, the 2 most common severe bleeding disorders.

475.1 Clinical and Laboratory Evaluation of Hemostasis

J. Paul Scott, Leslie J. Raffini, and Robert R. Montgomery

HISTORY
For most hemostatic disorders, the clinical history provides the most useful information. To evaluate for a bleeding disorder, the history should determine the site or sites of bleeding, the severity and duration of hemorrhage, and the age at onset. Was the bleeding spontaneous, or did it occur after trauma? Was there a previous personal or family history of similar problems? Did the symptoms correlate with the degree of injury or trauma? Does bruising occur spontaneously? Are there lumps with bruises for which there is minimal trauma? If the patient had previous surgery or significant dental procedures, was there any increased bleeding? If a child or adolescent has had surgery that affects the mucosal surfaces, such as a tonsillectomy or major dental extractions, the absence of bleeding usually rules out a hereditary bleeding disorder. Delayed or slow healing of superficial injuries may suggest a hereditary bleeding disorder. In postpubertal females, it is important to take a careful menstrual history. Because some common bleeding disorders, such as von Willebrand disease (VWD), have a fairly high prevalence, mothers and family members may have the same mild bleeding disorder and may not be cognizant that the child's menstrual history is abnormal. Women with mild VWD who have a moderate history of bruising frequently have a reduction of that bruising during pregnancy or after administration of oral contraceptives. Some medications, such as aspirin and other nonsteroidal antiinflammatory drugs, inhibit platelet function and increase bleeding symptoms in patients with a low platelet count or abnormal hemostasis. Standardized bleeding scores have been developed and are undergoing investigation for their sensitivity and specificity in children.

Outside the neonatal period, thrombotic disorders are relatively rare until adulthood. In the neonate, physiologic deficiencies of procoagulants and anticoagulants cause the hemostatic mechanism to be dysregulated, and clinical events can lead to either hemorrhage or thrombosis. If a child or teenager presents with deep venous thrombosis or pulmonary emboli, a detailed family history must be obtained to evaluate for deep venous thrombosis, pulmonary emboli, myocardial infarction, or stroke in other family members. The presence of thrombosis, especially in the absence of a provoking agent in the child or teenager, should induce the clinician to take a careful family history and consideration of evaluation for a hereditary or acquired predisposition to thrombosis.

PHYSICAL EXAMINATION
The physical examination should focus on whether bleeding symptoms are associated primarily with the mucous membranes or skin (mucocutaneous bleeding) or with the muscles and joints (deep bleeding). The examination should determine the presence of petechiae, ecchymoses, hematomas, hemorrhhroses, or mucous membrane bleeding. Patients with defects in platelet-blood vessel wall interaction (VWD or platelet function defects) usually have mucocutaneous bleeding, which may include epistaxis, menorrhagia, petechiae, ecchymoses, occasional hematomas, and, less commonly, hematuria and gastrointestinal bleeding. Individuals with a clotting factor deficiency of factor VIII or IX (hemophilia A or B) have symptoms of deep bleeding into muscles and joints, with much more extensive ecchymoses and hematoma formation. Patients with mild VWD or other mild bleeding disorders may have no abnormal findings on physical examination. Individuals with disorders of the collagen matrix and vessel wall may have loose joints and lax skin associated with easy bruising (Ehlers-Danlos syndrome).

Patients undergoing evaluation for thrombotic disorders should be asked about swollen, warm, tender extremities or internal organs (venous thrombosis), unexplained dyspnea or persistent “pneumonia,” especially in the absence of fever (pulmonary emboli), and varicosities and postphlebitic changes. Arterial thrombosis usually cause an acute, dramatic impairment of organ function, such as stroke, myocardial infarction, or a painful, white, cold extremity.

LABORATORY TESTS
In patients who have a positive bleeding history or who are actively hemorrhaging, a platelet count, PT, and partial thromboplastin time (PTT) should be performed as screening tests. In individuals with abnormal screening tests, further evaluation should be based upon those results. In a patient with an abnormal bleeding history and a positive family history, normal screening tests should not preclude further laboratory evaluation, which may include a thrombin time, VVF testing, and platelet function studies.

There are no routine screening tests for hereditary thrombotic disorders. If the family history is positive or clinical thrombosis is unexplained, specific thrombophilia assays should be performed. Thrombosis is rare in children, and when it is present, the possibility of a hereditary predisposition should be considered (see Chapter 478).

Platelet Count
Platelet count is essential in the evaluation of the child with a positive bleeding history because thrombocytopenia is the most common acquired cause of a bleeding diathesis in children. Patients with a platelet count of >50,000/mm³ rarely have significant clinical bleeding. Thrombocytosis in children is usually reactive and is not associated with bleeding or thrombotic complications. Persistent, severe thrombocytosis in the absence of an underlying illness may require evaluation for the very rare pediatric presentation of essential thrombocythemia or polycythemia vera.

Prothrombin Time and Activated Partial Thromboplastin Time
Because clotting factors were named in the order of discovery, they do not necessarily reflect the sequential order of activation (Table 475-1). In fact, factors III, IV, and VII were not subsequently found to be independent proteins; thus, these terms are no longer used. Only 2 factors have commonly used names: fibrinogen (factor I) and prothrombin (factor II). The dual mechanisms of activating clotting have been termed the intrinsic (surface activation) and extrinsic (tissue factor–mediated) pathways. Study of the hemostatic mechanism is further complicated in that the interactions in vivo may use different pathways from those studied in clinical laboratory testing. PT measures the activation of clotting by tissue factor (thromboplastin) in the presence of calcium. Addition of tissue factor causes a burst of factor VIIa generation. The tissue factor–factor VIIa complex activates factor X. Whether factor X is activated by the intrinsic or the extrinsic pathway, factor Xa on the platelet phospholipid surface complexes with factor V and calcium (the “prothrombinase” complex) to activate prothrombin to thrombin (also referred to as factor IIa). Once thrombin is generated, fibrinogen is converted to a fibrin clot, the end point of the reaction (see Fig. 475-2). PT is not prolonged with deficiencies of factors VIII, IX, XI, and XII. In most laboratories, the normal PT value is 10-13 sec. PT has been standardized using the international normalized ratio (INR) so that values can be compared from one laboratory or instrument to another. This ratio is used to determine similar degrees of anticoagulation with warfarin (Coumadin)-like medications.
Partial Thromboplastin Time
The intrinsic pathway involves the initial activation of factor XII, which is accelerated by 2 other plasma proteins, prekallikrein and high-molecular-weight kininogen. In the clinical laboratory, factor XII is activated using a surface (silica or glass) or a contact activator, such as ellagic acid. Factor XIIa, in turn, activates factor XI to factor XIa, which then catalyzes factor IX to factor IXa. On the platelet phospholipid surface, factor IXa complexes with factor VIII and calcium to activate factor X (“tenase” complex).

This process is accelerated by interaction with phospholipid and calcium at the steps involving factors V and VIII. An isolated deficiency of a single clotting factor may result in isolated prolongation of PT, PTT, or both, depending on the location of the factor in the clotting cascade. This approach is useful in determining hereditary clotting factor deficiencies; however, in acquired hemostatic disorders encountered in clinical practice, >1 clotting factor is frequently deficient, so the relative prolongation of PT and PTT must be assessed.

Measurement of PTT as performed in the clinical laboratory is actually “activated” PTT; however, most refer to it as PTT. This test measures the initiation of clotting at the level of factor XII through sequential steps to the final clot end point. It does not measure factor VII or factor X, or anticoagulants. PTT uses a contact activator (silica, kaolin, or ellagic acid) in the presence of calcium and phospholipid. Because of differences in reagents and laboratory instruments, the normal range for PTT varies among hospital laboratories. Normal ranges for PTT are much more variable from laboratory to laboratory than those for PT.

Thus, the mechanisms studied by PT and PTT allow the evaluation of clotting factor deficiencies, even though these pathways may not be the same as those occurring physiologically. In vivo, factor VIIa activates factors IX and X, but as routinely studied in the clinical laboratory, the pathway through which factor VIIa activates factor IX is not evaluated. If the tissue factor–factor VIIa complex activated only factor X, it would be difficult to explain why the most severe bleeding disorders are deficiencies of factor VIII (hemophilia A) and factor IX (hemophilia B). In vivo, thrombin is generated and feeds back to activate factor XI and accelerate the clotting process. Clotting in PTT can be prolonged by deficiencies of factor XII, prekallikrein, and high-molecular-weight kininogen, yet these deficiencies are asymptomatic conditions.

Thrombin Time
Thrombin time measures the final step in the clotting cascade, in which fibrinogen is converted to fibrin. The normal thrombin time varies between laboratories but is usually 11–15 sec. Prolongation of thrombin time occurs with reduced fibrinogen levels (hypofibrinogenemia or afibrinogenemia), with dysfunctional fibrinogen (dysfibrinogenemia), or in the presence of substances that interfere with fibrin polymerization, such as heparin and fibrin split products. If heparin contamination is a potential cause of prolonged thrombin time, a reptilase time is usually ordered. Alternatively, heparinase can be added to the sample and the thrombin time repeated.

Reptilase Time
Reptilase time uses snake venom to clot fibrinogen. Unlike thrombin time, reptilase time is not sensitive to heparin and is prolonged only by reduced or dysfunctional fibrinogen and fibrin split products. Therefore, if thrombin time is prolonged but reptilase time is normal, the prolonged thrombin time is due to heparin and does not indicate the presence of fibrin split products or reduced concentration or function of fibrinogen.

Mixing Studies
If there is unexplained prolongation of PT or PTT, a mixing study is usually performed. Normal plasma is added to the patient’s plasma, and the PT or PTT is repeated. Correction of PT or PTT by 1 : 1 mixing with normal plasma suggests deficiency of a clotting factor, because a 50% level of individual clotting proteins is sufficient to produce normal PT or PTT. If the clotting time is not corrected or only partially corrected, an inhibitor is usually present. An inhibitor of clotting may be either a chemical similar to heparin that delays coagulation or an antibody directed against a specific clotting factor or the phospholipid used in clotting tests. In the inpatient setting, the most common cause of this finding is heparin contamination of the sample. The presence of heparin in the sample can be ruled in or out either by addition of heparinase to the sample and repeating the thrombin time. If the mixing study is not corrected or if its result becomes more prolonged and the patient has clinical bleeding, an inhibitor of a specific clotting factor (antibody directed against the factor), most commonly factor VIII, factor IX, or factor XI, may be present. If the patient has no bleeding symptoms and both PTT and the mixing study are prolonged, a lupus-like anticoagulant (see Chapter 476) is often present. Patients with these findings usually have a long PTT, do not bleed, and may have a clinical predisposition to excessive clotting.

Bleeding Time
Bleeding time assesses the function of platelets and their interaction with the vascular wall. Disposable standardized devices have been developed that control the length and depth of the skin incision. A blood pressure cuff is applied to the upper arm and inflated to 40 mm Hg for children and adults. In term newborns and younger children, a modified device has been developed that is used with a lower blood pressure cuff pressure. Bleeding time is a difficult laboratory test to standardize, and there is much interlaboratory and interindividual variation. Although platelet counts of <100,000/mm³ are associated with prolonged bleeding time, disproportionate prolongation of

Table 475-1 Coagulation Factors

<table>
<thead>
<tr>
<th>CLOTTING FACTOR</th>
<th>SYNONYM</th>
<th>DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen</td>
<td>Congenital deficiency (afibrinogenemia) or dysfunction (dysfibrinogenemia)</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin</td>
<td>Congenital deficiency or dysfunction</td>
</tr>
<tr>
<td>V</td>
<td>Labile factor, proaccelerin</td>
<td>Congenital deficiency (parahemophilia)</td>
</tr>
<tr>
<td>VII</td>
<td>Stable factor or proconvertin</td>
<td>Congenital deficiency</td>
</tr>
<tr>
<td>VIII</td>
<td>Anthemophilic factor</td>
<td>Congenital deficiency is hemophilia A (classic hemophilia)</td>
</tr>
<tr>
<td>IX</td>
<td>Christmas factor</td>
<td>Congenital deficiency is hemophilia B (sometimes referred to as Christmas disease)</td>
</tr>
<tr>
<td>X</td>
<td>Stuart-Prower factor</td>
<td>Congenital deficiency</td>
</tr>
<tr>
<td>XI</td>
<td>Plasma thromboplastin antecedent</td>
<td>Congenital deficiency (sometimes referred to as hemophilia C)</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman factor</td>
<td>Congenital deficiency is not associated with clinical symptoms</td>
</tr>
<tr>
<td>XIII</td>
<td>Fibrin-stabilizing factor</td>
<td>Congenital deficiency</td>
</tr>
</tbody>
</table>
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bleeding time may suggest a qualitative platelet defect or VWD. Use of
the bleeding time is declining in many centers.

Platelet Function Analyzer

In an attempt to evaluate the early stages of hemostasis (platelet function and VWF interaction under high shear), several in vitro platelet
analyzers have been developed. The greatest experience has been with
the platelet function analyzer (PFA-100, Siemens Healthcare Diagnostics, Inc., Deerfield, IL). The PFA-100 measures platelet adhesionaggregation in whole blood at high shear when exposed to either
collagen-epinephrine or collagen-ADP. Results are reported as the
closure time measured in sec. The PFA-100 appears to be sensitive to
severe forms of VWD and platelet dysfunction. The PFA-100 has variable sensitivity, particularly in the detection of mild VWD and some
platelet function defects. Its use as a preoperative screening tool has
been disappointing in some studies.

D-Dimer

D-dimer is formed by plasmin degradation of crosslinked fibrin, produced when fibrinogen is clotted by thrombin and cross-linked by
Table 475-2

◆

Hemostasis ﻿2383

factor XIIIa and is more specific for fibrinolysis than fibrin degradation
products. D-dimer is elevated in patients with disseminated intravascular coagulation or acute deep vein thrombosis but is relatively nonspecific in that other ill hospitalized patients often have elevated levels
of D-dimer. Adult studies show that the D-dimer can be useful to help
exclude venous thrombosis and pulmonary embolus because of its high
negative predictive value; for example, a patient with a normal D-dimer
value is unlikely to have an acute thrombosis.

Clotting Factor Assays

Each of the clotting factors can be measured in the clinical laboratory
using individual factor–deficient plasmas. For most clotting factors,
activity is measured against pooled normal plasma or against a standard, by which 100% activity is expressed as 100 IU/dL. By definition,
1 IU of each factor is defined as that amount in 1 mL of normal plasma
referenced against a standard established by the World Health Organization. For most clotting factors, the normal range is 50-150 IU/dL
(50-150%) (Table 475-2).
In patients with hemophilia A or hemophilia B, inhibitors of factor
VIII or factor IX may develop after exposure to replacement therapy.

Reference Values for Coagulation Tests in Healthy Children*

TEST
SCREENING TESTS
Prothrombin time
(sec)
Activated partial
thromboplastin time
(sec)
Bleeding time (min)
PROCOAGULANTS
Fibrinogen
Factor II
Factor V
Factor VII
Factor VIII
procoagulant
von Willebrand factor
Factor IX
Factor X
Factor XI
Factor XII
Prekallikrein
High-molecularweight kininogen
Factor XIIIa|
Factor XIIIb|
ANTICOAGULANTS
Antithrombin-III
Protein C
Protein S:
Total (units/mL)
Free (units/mL)
Plasminogen (units/
mL)
Tissue-type
plasminogen
activator (ng/mL)
Antiplasmin (units/mL)
Plasminogen activator
inhibitor-I

28-31 Wk
GESTATION

30-36 Wk
GESTATION

15.4 (14.6-16.9) 13.0 (10.6-16.2)
108 (80-168)

53.6 (27.5-79.4)‡§

FULL TERM

1-5 Yr

13.0 (10.1-15.9)

11 (10.6-11.4)

42.9 (31.3-54.3)‡

30 (24-36)
6 (2.5-10)‡

6-10 Yr

11-18 Yr

11.1 (10.1-12.0) 11.2 (10.2-12.0)
31 (26-36)
7 (2.5-13)‡

ADULT
12 (11.0-14.0)

32 (26-37)

33 (27-40)

5 (3-8)‡

4 (1-7)

256
31
65
37
79

(160-550)
(19-54)
(43-80)
(24-76)
(37-126)

243
45
88
67
111

(150-373)‡§
(20-77)‡
(41-144)§
(21-113)‡
(5-213)

283
48
72
66
100

(167-399)
(26-70)‡
(34-108)‡
(28-104)‡
(50-178)

276
94
103
82
90

(170-405)
(71-116)‡
(79-127)
(55-116)‡
(59-142)

279
88
90
86
95

(157-400)
(67-107)‡
(63-116)‡
(52-120)‡
(58-132)

300
83
77
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(154-448)
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(55-99)‡
(58-115)‡
(53-131)

278
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106
105
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(156-40)
(70-146)
(62-150)
(67-143)
(50-149)

141
18
36
23
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(83-223)
(17-20)
(25-64)
(11-33)
(5-35)
(15-32)
(19-52)

136
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33
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(78-210)
(19-65)‡§
(11-71)‡
(8-52)‡§
(10-66)‡§
(9-89)‡
(9-89)‡

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(50-287)
(15-91)†‡
(12-68)‡
(40-66)‡
(13-93)‡
(18-69)‡
(6-102)‡

82
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(58-116)‡
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(65-130)
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95
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(44-144)
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(55-101)‡
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(60-130)

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(46-153)
(59-122)‡
(50-117)
(50-97)‡
(34-137)‡
(53-145)
(63-119)

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(50-158)
(55-163)
(70-152)
(56-150)
(52-164)
(62-162)
(50-136)

28 (20-38)

70 (32-108)‡
81 (35-127)‡

79 (27-131)‡
76 (30-122)‡

108 (72-143)
113 (69-156)‡

109 (65-151)
116 (77-154)‡

99 (57-140)
102 (60-143)

105 (55-155)
98 (57-137)

38 (14-62)‡§
28 (12-44)‡§

63 (39-87)‡
35 (17-53)‡

111 (82-139)
66 (40-92)‡

111 (90-131)
69 (45-93)‡

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83 (55-111)‡

100 (74-126)
96 (64-128)

26 (14-38)‡§

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195 (125-265)

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98 (78-118)

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42 (22-62)
92 (75-108)

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86 (68-103)

81 (61-113)
45 (27-61)
99 (77-122)

8.48 (3.00-16.70)

9.6 (5.0-18.9)

2.15 (1.0-4.5)‡

2.42 (1.0-5.0)‡

2.16 (1.0-4.0)‡

1.02 (0.68-1.36)

78 (40-116)
5.4 (0.0-12.2)‡

85 (55-115)
6.4 (2.0-15.1)

105 (93-117)
5.42 (1.0-10.0)

99 (89-110)
6.79 (2.0-12.0)‡

98 (78-118)
6.07 (2.0-10.0)‡

102 (68-136)
3.60 (0.0-11.0)

*All factors except fibrinogen are expressed as units/mL (fibrinogen in mg/mL), in which pooled normal plasma contains 1 unit/mL. All data are expressed as the
mean, followed by the upper and lower boundaries encompassing 95% of the normal population (shown in parentheses). Normal ranges above vary based on the
reagents and instruments used.
†
Levels for 19-27 wk and 28-31 wk gestation are from multiple sources and cannot be analyzed statistically.
‡
Values are significantly different from those of adults.
§
Values are significantly different from those of full-term infants.
|
Value given as CTA (Committee on Thrombolytic Agents) units/mL. Normal ranges above vary based on the reagents and instruments used.
Data from Andrew M, Paes B, Johnston M: Development of the hemostatic system in the neonate and young infant, Am J Pediatr Hematol Oncol 12:95, 1990; and


To quantitate the amount of inhibitor present, the standardized clinical assay of these clotting inhibitors is the Bethesda assay. One Bethesda unit is defined as the amount that will inhibit 50% of the clotting factor in normal plasma.

**Platelet Aggregation**

When a qualitative platelet function defect is suspected, platelet aggregation testing is usually ordered. Platelet-rich plasma from the patient is activated with 1 of a series of agonists (ADP, epinephrine, collagen, thrombin or thrombin-receptor peptide, and ristocetin). Some platelet aggregometers measure specific adenosine triphosphate release from the platelets, as reflected in generating luminescence (lumiaggrometer), and are more sensitive in detecting abnormalities of the platelet release reaction from storage granules. Repeat testing or testing of other symptomatic family members can help to determine the hereditary nature of the defect. Many medications, especially aspirin, other nonsteroidal antiinflammatory drugs, and valproic acid, alter platelet function testing. Figure 475-1 provides an approach to the differential diagnosis of many common bleeding disorders based on screening tests.

**Testing for Thrombotic Predisposition**

Hereditary predisposition to thrombosis is associated with a reduction of anticoagulant function (protein C, protein S, AT-III); the presence of a factor V molecule that is resistant to inactivation by protein C (factor V Leiden); elevated levels of procoagulants (a mutation of the prothrombin gene); or a deficiency of fibrinolysis (plasminogen deficiency); and the rare metabolic disease homocystinuria. When patients are being screened for prothrombotic tendencies, specific tests of the natural anticoagulants and polymerase chain reaction analysis for common prothrombotic mutations are warranted. Although both immunologic and functional tests are usually available, functional assays of protein C, protein S, and AT-III are clinically more useful.

**Factor V Leiden**

is a common mutation in factor V that is associated with an increased risk of thrombosis. A point mutation in the factor V molecule prevents the inactivation of factor Va by activated protein C and, thereby, the persistence of factor Va. This defect, also known as activated protein C resistance, is easily diagnosed with DNA testing.

The **prothrombin gene mutation (G20210A)** is a mutation in the noncoding portion of the prothrombin gene, with a glycine (G) at position 20210 being replaced by an alanine (A). This mutation increases the amount of prothrombin messenger RNA, is associated with elevations of prothrombin, and causes a predisposition to thrombosis. This abnormality is easily identified with molecular diagnostic (DNA) testing.

**Elevated Homocysteine**

Levels of homocysteine may be increased as a result of genetic mutations, causing homocystinuria. Patients with homocysteine elevation are predisposed to arterial and venous thrombosis as well as to an increase in arteriosclerosis.

**Tests of the Fibrinolytic System**

Euglobulin clot lysis time is a screening test used in some laboratories to assess fibrinolysis. More specific tests are available in most laboratories to determine the levels of plasminogen, plasminogen activator, and inhibitors of fibrinolysis. An increase in fibrinolysis may be associated with hemorrhagic symptoms, and a delay in fibrinolysis is associated with thrombosis.

**DEVELOPMENTAL HEMOSTASIS**

The normal newborn infant has reduced levels of most procoagulants and anticoagulants (see Table 475-1). In general, there is a more marked abnormality in the preterm infant. Although major differences exist in the normal ranges for newborn and preterm infants, these ranges vary greatly among laboratories based upon the instruments and reagents used. During gestation, there is progressive maturation and increase of the clotting factors synthesized by the liver. The extremely premature infant has prolonged PT and PTT values as well as a marked reduction in anticoagulant protein levels (protein C, protein S, and AT-III). Levels of fibrinogen, factors V and VIII, VWF, and platelets are near-normal throughout the later stages of gestation (see Chapter 103.4). Because protein C and protein S are physiologically reduced, the normal factors V and VIII are not balanced with their regulatory proteins. In contrast, the physiologic deficiency of vitamin K–dependent procoagulant proteins (factors II, VII, IX, and X) is partially balanced by the physiologic reduction of AT-III. The net effect is that newborns (especially premature infants) are at increased risk for complications of bleeding, clotting, or both.
Bibliography


Hereditary Clotting Factor Deficiencies (Bleeding Disorders)

J. Paul Scott and Veronica H. Flood

Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are the most common and serious congenital coagulation factor deficiencies. The clinical findings in hemophilia A and hemophilia B are virtually identical. Hemophilia C is the bleeding disorder associated with reduced levels of factor XI (see Chapter 476.2). Reduced levels of the contact factors (factor XII, high-molecular-weight kininogen, and prekallikrein) are associated with significant prolongation of activated partial thromboplastin time (aPTT; also referred to as PTT), but are not associated with hemorrhage, as discussed in Chapter 476.3. Other coagulation factor deficiencies that are less common are briefly discussed in subsequent subchapters.

476.1 Factor VIII or Factor IX Deficiency (Hemophilia A or B)

J. Paul Scott

Deficiencies of factors VIII and IX are the most common severe inherited bleeding disorders. Recombinant factor VIII and factor IX concentrates are available to treat patients with hemophilia and thereby avoid the infectious risk of plasma-derived transfusion-transmitted diseases.

PATHOPHYSIOLOGY

Factors VIII and IX participate in a complex required for the activation of factor X. Together with phospholipid and calcium, they form the “tenase,” or factor X–activating, complex. Figure 475-1 in Chapter 475 shows the clotting process as it occurs in the test tube, with factor X being activated by either the complex of factors VIII and IX or the complex of tissue factor and factor VII. In vivo, the complex of factor VIIa and tissue factor activates factor IX to initiate clotting. In the laboratory, prothrombin time (PT) measures the activation of factor X by factor VII and is therefore normal in patients with factor VIII or factor IX deficiency.
After injury, the initial hemostatic event is formation of the platelet plug, together with the generation of the fibrin clot that prevents further hemorrhage. In hemophilia A or B, clot formation is delayed and is not robust. Inadequate thrombin generation leads to failure to form a tightly crosslinked fibrin clot to support the platelet plug. Patients with hemophilia slowly form a soft, friable clot. When untreated bleeding occurs in a closed space, such as a joint, cessation of bleeding may be the result of tamponade. With open wounds, in which tamponade cannot occur, profuse bleeding may result in significant blood loss. The clot that is formed may be friable, and rebleeding occurs during the physiologic lysis of clots or with minimal new trauma.

**CLINICAL MANIFESTATIONS**

Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus. Only 2% of neonates with hemophilia sustain intracranial hemorrhages, and 30% of male infants with hemophilia bleed with circumcision. Thus, in the absence of a positive family history (hemophilia has a high rate of spontaneous mutation), hemophilia may go undiagnosed in the newborn. Obvious symptoms such as easy bruising, intramuscular hematomas, and hemarthroses begin when the child begins to cruise. Bleeding from minor traumatic lacerations of the mouth (a torn frenulum) may persist for hours or days and may cause the parents to seek medical evaluation. Even in patients with severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age. Although bleeding may occur in any area of the body, the hallmark of hemophilic bleeding is hemarthrosis. Bleeding into the joints may be induced by minor trauma; many hemarthroses are spontaneous. The earliest joint hemorrhages appear most commonly in the ankle. In the older child and adolescent, hemarthroses of the knees and elbows are also common. Whereas the child's early joint hemorrhages are recognized only after major swelling and fluid accumulation in the joint space, older children are frequently able to recognize bleeding before the physician does. They complain of a warm, tingling sensation in the joint as the first sign of an early joint hemorrhage. Repeated bleeding episodes into the same joint in a patient with severe hemophilia may become a "target" joint. Recurrent bleeding may then become spontaneous because of the underlying pathologic changes in the joint.

Although most muscular hemorrhages are clinically evident owing to localized pain or swelling, bleeding into the iliopsoas muscle requires specific mention. A patient may lose large volumes of blood into the iliopsoas muscle, verging on hypovolemic shock, with only a vague area of referred pain in the groin. The hip is held in a flexed, internally rotated position owing to irritation of the iliopsoas. The diagnosis is made clinically from the inability to extend the hip but must be confirmed with ultrasonography or CT (Fig. 476-1). Life-threatening bleeding in the patient with hemophilia is caused by bleeding into vital structures (central nervous system, upper airway) or by exsanguination (external trauma, gastrointestinal or iliopsoas hemorrhage). Prompt treatment with clotting factor concentrate for these life-threatening hemorrhages is imperative. If head trauma is of sufficient concern to suggest radiologic evaluation, factor replacement should precede radiologic evaluation. Simply put: “Treat first, image second!” Life-threatening hemorrhages require replacement therapy to achieve a level equal to that of normal plasma (100 IU/dL, or 100%).

Patients with mild hemophilia who have factor VIII or factor IX levels >5 IU/dL usually do not have spontaneous hemorrhages. These individuals may experience prolonged bleeding after dental work, surgery, or injuries from moderate trauma and may not be diagnosed until they are older.

**LABORATORY FINDINGS AND DIAGNOSIS**

The laboratory screening test that is affected by a reduced level of factor VIII or factor IX is PTT. In severe hemophilia, the PTT value is usually 2–3 times the upper limit of normal. Results of the other screening tests of the hemostatic mechanism (platelet count, bleeding time, prothrombin time, and thrombin time) are normal. Unless the patient has an inhibitor to factor VIII or IX, the mixing of normal plasma with patient plasma results in correction of PTT value. The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia. If correction does not occur on mixing, an inhibitor may be present. In 25–35% of patients with hemophilia who receive infusions of factor VIII or factor IX, a factor-specific antibody may develop. These antibodies are directed against the active clotting site and are termed inhibitors. In such patients, the quantitative Bethesda assay for inhibitors should be performed to measure the antibody titer.

**DIFFERENTIAL DIAGNOSIS**

In young infants with severe bleeding manifestations, the differential diagnosis includes severe thrombocytopenia; severe platelet function...
disorders, such as Bernard-Soulier syndrome and Glanzmann thrombocytopenia; type 3 (severe) von Willebrand disease; and vitamin K deficiency. Hemostatic screening tests should differentiate these entities from hemophilia.

GENETICS AND CLASSIFICATION
Hemophilia occurs in approximately 1:5,000 males, with 85% having factor VIII deficiency and 10-15% having factor IX deficiency. Hemophilia shows no apparent racial predilection, appearing in all ethnic groups. The severity of hemophilia is classified on the basis of the patient's baseline level of factor VIII or factor IX, because factor levels usually correlate with the severity of bleeding symptoms. By definition, 1 IU of each factor is defined as that amount in 1 mL of normal plasma referenced against a standard established by the World Health Organization (WHO); thus, 100 mL of normal plasma has 100 IU/dL (100% activity) of each factor. For ease of discussion, henceforth in this chapter, we use the term % activity to refer to the percentage found in normal plasma (100% activity). Factor concentrates are also referenced against an international WHO standard, so treatment doses are usually referred to in IU. Severe hemophilia is characterized as having <1% activity of the specific clotting factor, and bleeding is often spontaneous. Patients with moderate hemophilia have factor levels of 1-5% and usually require mild trauma to induce bleeding. Individuals with mild hemophilia have levels >5%, may go many years before the condition is diagnosed, and frequently require significant trauma to cause bleeding. The hemostatic level for factor VIII is >30-40%, and for factor IX, it is >25-30%. The lower limit of levels for factors VIII and IX in normal individuals is approximately 50%.

The genetics for factors VIII and IX are carried near the terminus of the long arm of the X chromosome and are therefore X-linked traits. The majority of patients with hemophilia have reduced clotting factor protein; 5-10% of those with hemophilia A and 40-50% of those with hemophilia B make a dysfunctional protein. Approximately 45-50% of patients with severe hemophilia A have the same mutation, in which there is an internal inversion within the factor VIII gene that results in production of no protein. This mutation can be detected in the blood of patients or carriers and in the amniotic fluid by molecular techniques. African-Americans often have a different factor VIII haplotype, and this difference may be the reason that African-Americans have higher inhibitor formation (see later). Because of the multiple genetic causes of either factor VIII or factor IX deficiency, most cases of hemophilia are classified according to the amount of factor VIII or factor IX clotting activity. In the newborn, factor VIII values may be artificially elevated because of the acute-phase response elicited by the birth process. This artificial elevation may cause a mildly affected patient to have normal or near-normal levels of factor VIII. Patients with severe hemophilia do not have detectable levels of factor VIII. In contrast, factor IX levels are physiologically low in the newborn. If severe hemophilia is present in the family, an undetectable level of factor IX is diagnostic of severe hemophilia B. In some patients with mild factor IX deficiency, the presence of hemophilia can be confirmed only after several weeks of life.

Through lyonization of the X chromosome, some female carriers of hemophilia A or B have sufficient reduction of factor VIII or factor IX to produce mild bleeding disorders. Levels of these factors should be determined in all known or potential carriers to assess the need for treatment in the event of surgery or clinical bleeding.

Because factor VIII is carried in plasma by von Willebrand factor, the ratio of factor VIII to von Willebrand factor is sometimes used to diagnose carriers of hemophilia. When possible, specific genetic mutations should be identified in the propositus and used to test other family members who are at risk of either having hemophilia or being carriers.

TREATMENT
Early, appropriate therapy is the hallmark of excellent hemophilia care. When mild to moderate bleeding occurs, values of factor VIII or factor IX must be raised to hemostatic levels, in the 35-50% range. For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity.

Calculation of the dose of recombinant factor VIII (FVIII) or recombinant factor IX (FIX) is as follows:

Dose of rFVIII (IU) = \% desired (rise in rFVIII) \times Body weight (kg) \times 0.5

Dose of rFIX (IU) = \% desired (rise in plasma FIX) \times Body weight (kg) \times 1.4

For factor VIII, the correction factor is based on the volume of distribution of factor VIII. For factor IX, the correction factor is based on the volume of distribution and the observed rise in plasma level after infusion of recombinant factor IX.

Table 476-1 summarizes the treatment of some common types of hemorrhage in a patient with hemophilia.

With the availability of recombinant replacement products, prophylaxis is the standard of care for most children with severe hemophilia, to prevent spontaneous bleeding and early joint deformities. In addition to currently available recombinant factors, products are being developed to increase the plasma half-life and reduce the immunogenicity of hemostatic factors. A study comparing prophylaxis with aggressive episodic treatment provides evidence for the superiority of prophylaxis in preventing debilitating joint disease. If target joints develop, “secondary” prophylaxis is often initiated.

With mild factor VIII hemophilia, the patient’s endogenously produced factor VIII can be released by the administration of desmopressin acetate. In patients with moderate or severe factor VIII deficiency, the stored levels of factor VIII in the body are inadequate, and desmopressin treatment is ineffective. The risk of exposing the patient with mild hemophilia to transfusion-transmitted diseases and the cost of recombinant products warrant the use of desmopressin, if it is effective. A concentrated intranasal form of desmopressin acetate, not the enuresis or pituitary replacement dose, can also be used to treat patients with mild hemophilia A. The dose is 150 µg (1 puff) for children weighing <50 kg and 300 µg (2 puffs) for children and young adults weighing >50 kg. Most centers administer a trial of desmopressin to determine the level of factor VIII achieved after its infusion. Desmopressin is not effective in the treatment of factor IX–deficient hemophilia.

Preliminary trials of an adeno-associated virus vector containing the factor IX gene are underway with some encouraging initial results.

PROPHYLAXIS
Many patients are now given lifelong prophylaxis to prevent spontaneous joint bleeding. The National Hemophilia Foundation recommends that prophylaxis be considered optimal therapy for children with severe hemophilia. Usually, such programs are initiated with the first joint hemorrhage. Young children often require the insertion of a central catheter to ensure venous access. Such programs are expensive but are highly effective in preventing or greatly limiting the degree of joint pathology; however, complications include central line infection and thrombosis. Treatment is usually provided every 2-3 days to maintain a measurable plasma level of clotting factor (1-2%) when assayed just before the next infusion (trough level). Whether prophylaxis should be continued into adulthood has not yet been adequately studied. If moderate arthropathy develops, prevention of future bleeding will require higher plasma levels of clotting factors. In the older child who is not given primary prophylaxis, secondary prophylaxis is frequently initiated if a target joint develops.

SUPPORTIVE CARE
Although it is easy to tell parents that their child should avoid trauma, this advice is not practical in active children and adolescents. Toddlers are active, are curious about everything, and injure themselves easily. Effective measures include anticipatory guidance, including the use of car seats, seatbelts, and bike helmets, and the importance of avoiding high-risk behaviors. Older boys should be counseled to avoid violent contact sports, but this issue is a challenge. Boys with severe hemophilia often sustain hemorrhages in the absence of known trauma. Early psychosocial intervention helps the family achieve a balance.
between overprotection and permissiveness. Patients with hemophilia should avoid aspirin and other nonsteroidal antiinflammatory drugs that affect platelet function. The child with a bleeding disorder should receive the appropriate vaccinations against hepatitis B, even though recombinant products may avoid exposure to transfusion-transmitted diseases. Patients exposed to plasma-derived products should be screened periodically for hepatitis B and C, HIV, and abnormalities in liver function.

**CHRONIC COMPLICATIONS**

Long-term complications of hemophilia A and B include chronic arthropathy, the development of an inhibitor to either factor VIII or factor IX, and the risk of transfusion-transmitted infectious diseases. Although an aggressive, or prophylactic, approach to treatment has reduced the problems of chronic arthropathy, these problems have not been eliminated.

Historically, chronic arthropathy has been the major long-term disability associated with hemophilia. The natural history of untreated hemophilia is one of cyclic recurrent hemorrhages into specific joints, including hemmorhages into the same (target) joint. In young children, the joint distends easily and a large volume of blood may fill the joint until tamponade ensues or therapy intervenes. After joint hemorrhage, proteolytic enzymes are released by white blood cells into the joint space, and heme iron induces macrophage proliferation, leading to inflammation of the synovium. The synovium thickens and develops frondlike projections into the joint that are susceptible to being pinched and may induce further hemorrhage. The cartilaginous surface becomes eroded and ultimately may even expose raw bone, leaving the joint susceptible to articular fusion. In the older patient with advanced arthropathy, bleeding into the target joint, with its thickened synovium, causes severe pain, because the joint may have little space to accommodate blood. Once a target joint is seen to be developing, the patient is usually given short- or long-term prophylaxis to prevent progression of the arthropathy and reduce inflammation.

**Inhibitor Formation**

Infusion of the deficient clotting factor may initiate an immune response in patients with either factor VIII or factor IX deficiency. Inhibitors are antibodies directed against factor VIII or factor IX that block the clotting activity. Failure of a bleeding episode to respond to appropriate replacement therapy is usually the first sign of an inhibitor. Less often, inhibitors are identified during routine follow-up screening for inhibitors. Inhibitors develop in approximately 25-35% of patients with hemophilia A; the percentage is somewhat lower in patients with hemophilia B, many of whom make an inactive dysfunctional protein that renders them less susceptible to an immune response. Highly purified factor IX or recombinant factor IX seems to increase the frequency of inhibitor development, and some anti–factor IX inhibitors induce anaphylaxis. Many patients who have an inhibitor lose it with continued regular infusions. Others have a higher titer of antibody with subsequent infusions and may need to go through desensitization (immune tolerance induction) programs, in which high doses of factor VIII for hemophilia A or factor IX for hemophilia B are infused in an attempt to saturate the antibody and permit the body to develop tolerance. Factor IX immune tolerance programs have resulted in nephrotic syndrome in some patients. Rituximab has been used,

<table>
<thead>
<tr>
<th>TYPE OF HEMORRHAGE</th>
<th>HEMOPHILIA A</th>
<th>HEMOPHILIA B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemarthrosis*</td>
<td>50-60 IU/kg factor VIII concentrate† on day 1; then 20-30 IU/kg on days 2, 3, 5 until joint function is normal or back to baseline. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.</td>
<td>80-100 IU/kg on day 1; then 40 IU/kg on days 2, 4. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.</td>
</tr>
<tr>
<td>Muscle or significant subcutaneous hematoma</td>
<td>50 IU/kg factor VIII concentrate; 20 IU/kg every-other-day treatment may be needed until resolved</td>
<td>80 IU/kg factor IX concentrate‡; treatment every 2-3 days may be needed until resolved</td>
</tr>
<tr>
<td>Mouth, deciduous tooth, or tooth extraction</td>
<td>20 IU/kg factor VIII concentrate; antifibrinolytic therapy; remove loose deciduous tooth</td>
<td>40 IU/kg factor IX concentrate‡; antifibrinolytic therapy; remove loose deciduous tooth</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy; 20 IU/kg factor VIII concentrate if this treatment fails</td>
<td>Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy; 30 IU/kg factor IX concentrate if this treatment fails</td>
</tr>
<tr>
<td>Major surgery, life-threatening hemorrhage</td>
<td>50-75 IU/kg factor VIII concentrate, then initiate 25 IU/kg q8-12h to maintain trough level &gt;50 IU/dL for 5-7 days, then 50 IU/kg q24h to maintain trough &gt;25 IU/dL for 7 days</td>
<td>120 IU/kg factor IX concentrate‡; then 50-60 IU/kg every 12-24 hr to maintain factor IX at &gt;40 IU/dL for 5-7 days, and then at &gt;30 IU/dL for 7 days</td>
</tr>
<tr>
<td>Iliopsoas hemorrhage</td>
<td>50 IU/kg factor VIII concentrate, then 25 IU/kg every 12 hr until asymptomatic; then 20 IU/kg every other day for a total of 10-14 days**</td>
<td>120 IU/kg factor IX concentrate‡; then 50-60 IU/kg every 12-24 hr to maintain factor IX at &gt;40 IU/dL until patient is asymptomatic; then 40-50 IU/kg every other day for a total of 10-14 days***</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Bed rest; 1.5x maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected)</td>
<td>Bed rest; 1.5x maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate‡; if not controlled, give prednisone (unless patient is HIV-infected)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>20-40 IU/kg factor VIII concentrate every other day to achieve a trough level ≥1%</td>
<td>30-50 IU/kg factor IX concentrate† every 2-3 days to achieve a trough level ≥1%</td>
</tr>
</tbody>
</table>

*For hip hemarthrosis, orthopedic evaluation for possible aspiration is advisable to prevent avascular necrosis of the femoral head.
†For mild or moderate hemophilia, desmopressin, 0.3 µg/kg, should be used instead of factor VIII concentrate, if the patient is known to respond with a hemostatic level of factor VIII; if repeated doses are given, monitor factor VIII levels for tachyplyaxis.
‡Stated doses apply for recombinant factor IX concentrate; for plasma-derived factor IX concentrate, use 70% of the stated dose.
§For blood urea nitrogen >90 mg/dL (54 mmol/L), start diuresis and consider hemodialysis.
††If repeated doses of factor IX concentrate are required, use highly purified, specific factor IX concentrate.

Factor XI deficiency is an autosomal deficiency associated with mild to moderate bleeding symptoms. It is frequently encountered in Ashkenazi Jews but has been found in many other ethnic groups. In Israel, 1-3/1,000 individuals are homozygous for this deficiency.

The bleeding tendency is not as severe as in factor VIII or factor IX deficiency. The bleeding associated with factor XI deficiency is not correlated with the amount of factor XI. Some patients with severe deficiency may have minimal or no symptoms at the time of major surgery. Because factor XI augments thrombin generation and leads to activation of the fibrinolytic inhibitor thrombin-activatable fibrinolysis inhibitor, surgical bleeding is more prominent in sites of high fibrinolytic activity like the oral cavity. Unless the patient previously had surgery without bleeding, replacement therapy should be considered and given preoperatively, depending on the nature of the surgical procedure. No approved concentrate of factor XI is available in the United States; therefore, the physician must use fresh-frozen plasma (FFP).

Bleeding during minor surgery can be controlled with local pressure. Patients undergoing dental extractions can be monitored closely and may benefit from treatment with fibrinolytic inhibitors like aminocaproic acid, with plasma replacement therapy used only if hemorrhage occurs. In a patient with homozygous deficiency of factor XI, PT is often longer than it is in patients with either severe factor VIII or factor IX deficiency. The paradox of fewer clinical symptoms in combination with longer PTT is surprising, but it occurs because factor VIIa can activate factor IX in vivo. The deficiency of factor XI can be confirmed by specific factor XI assays. Plasma infusions of 1 IU/kg usually increase the plasma concentration by 2%. Thus, infusion of plasma at 10-15 mL/kg will result in a plasma level of 20-30%, which is usually sufficient to control moderate hemorrhage. Frequent infusions of plasma would be necessary to achieve higher levels of factor XI. Because the half-life of factor XI is usually ≥48 hr, maintaining adequate levels of factor XI commonly is not difficult.

Deficiency of the “contact factors” (factor XII, prekallikrein, and high-molecular-weight kininogen) causes prolonged PTT but no bleeding symptoms. Because these contact factors function at the step of initiation of the intrinsic clotting system by the reagent used to determine PTT, the PTT is markedly prolonged when these factors are absent. Thus, there is the paradoxical situation in which PTT is extremely prolonged with no evidence of clinical bleeding. It is important that individuals with these findings be well informed about the meaning of their clotting factor deficiency because they do not need treatment, even for major surgery.
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Bibliography


Bibliography
Bibliography
476.6 Prothrombin (Factor II) Deficiency  
J. Paul Scott

Prothrombin deficiency is caused either by a markedly reduced prothrombin level (hypoprothrombinemia) or by functionally abnormal prothrombin (dysprothrombinemia). Laboratory testing in homozygous patients shows prolonged PT and PTT. Factor II, or prothrombin, assays show a markedly reduced prothrombin level. Mucocutaneous bleeding in infancy and posttraumatic bleeding later are common. Patients are treated with either FFP or, rarely, prothrombin complex concentrates. In prothrombin deficiency, FFP is useful, because the half-life of prothrombin is 3.5 days. Administration of 1 IU/kg of prothrombin will increase the plasma activity by 1%.

Bibliography is available at Expert Consult.

476.7 Factor V Deficiency  
J. Paul Scott

Deficiency of factor V is an autosomal recessive, mild to moderate bleeding disorder that has also been termed parahemophilia. Hemarthroses occur rarely; mucocutaneous bleeding and hematomas are the most common symptoms. Severe menorrhagia is a frequent symptom in women. Laboratory evaluation shows prolonged PTT and PT. Specific assays for factor V show a reduction in factor V levels. FFP is the only currently available therapeutic product that contains factor V. Factor V is lost rapidly from stored FFP. Patients with severe factor V deficiency are treated with infusions of FFP at 10 mL/kg every 12 hr. Rarely, a patient with a negative family history of bleeding has an acquired antibody to factor V. Often, such a patient does not bleed because the factor V in platelets prevents excessive bleeding.

Bibliography is available at Expert Consult.

476.8 Combined Deficiency of Factors V and VIII  
J. Paul Scott

Combined deficiency of factors V and VIII occurs secondary to the absence of an intracellular transport protein that is responsible for transporting factors V and VIII from the endoplasmic reticulum to the Golgi compartments. This explains the paradoxical deficiency of 2 factors, one encoded on chromosome 1 and the other on the X chromosome. Bleeding symptoms are often milder than for hemophilia A and are treated with FFP to replace both factors V and VIII.

476.9 Fibrinogen (Factor I) Deficiency  
J. Paul Scott

Congenital dysfibrinogenemia is a rare autosomal recessive disorder in which there is an absence of fibrinogen. Patients with this disorder do not bleed as frequently as patients with hemophilia and rarely have hemarthroses. Affected patients may present in the neonatal period with gastrointestinal hemorrhage or hematomas after vaginal delivery. In addition to marked prolongation of PT and PTT, thrombin time is prolonged. In the absence of consumptive coagulopathy, an unmeasur-
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**Bibliography**


Bibliography


von Willebrand disease (VWD) is the most common inherited bleeding disorder, with an estimated prevalence cited at 1:100 to 1:10,000 depending on the criteria used for diagnosis. Patients with VWD typically present with mucosal bleeding. A family history of either VWD or bleeding symptoms and confirmatory laboratory testing are also required for the diagnosis of VWD.

**PATHOPHYSIOLOGY**

VWD is caused by a defect in von Willebrand factor (VWF). VWF has several functions in coagulation. First, VWF serves to tether platelets to injured subendothelium via binding sites for platelets and for collagen. Second, VWF serves as a carrier protein for factor VIII (FVIII), protecting FVIII from degradation in plasma. VWF is stored in endothelial cells and in platelet Weibel-Palade bodies and circulates as a large multimeric glycoprotein. Shear stress induces a conformational change in VWF that facilitates its ability to bind platelets through a binding site on platelet glycoprotein Ib (GPIb). This enables VWF to recruit platelets to the site of clot formation, a function that is dependent on the high-molecular-weight multimer forms of VWF.

VWD typically presents with mucosal bleeding, similar to that seen with other platelet defects. Epistaxis, easy bruising, and menorrhagia in women are common complaints. Symptoms, however, are variable, and do not necessarily correlate well with VWF levels. Surgical bleeding, particularly with dental extractions or adenotonsillectomy, is another common presentation. Severe type 3 VWD may present with joint bleeds. Most patients will have a family history of bleeding. Women are more likely to be diagnosed with VWD because of the potential for symptoms with menorrhagia, but men and women are equally likely to have VWD. Diagnosis based on symptoms may be difficult, however, as minor bruising and epistaxis are not uncommon in childhood. Significant unexplained bruising is more often from nonaccidental trauma than from an underlying bleeding disorder.

**CLASSIFICATION**

VWD may be caused by quantitative or qualitative defects in VWF. Mild to moderate quantitative defects are classified as type 1 VWD, while severe quantitative defects, in which there is no detectable VWF protein, are classified as type 3 VWD. The qualitative defects are grouped together as type 2 VWD.

Type 1 VWD is by far the most common type, accounting for 60-80% of all VWD patients. Typical symptoms include mucosal bleeding, such as epistaxis and menorrhagia as well as easy bruising, and decreased VWF activity in terms of platelet binding. It is the most common of the type 2 variants, accounting for approximately 10% of VWD cases. Type 2A VWD can result from mutations that affect multimer assembly and processing, or mutations that result in increased proteolysis of secreted VWF. Some mutations affect both secretion and clearance of the VWF. Regardless of the mechanism, all type 2A VWD patients lack the high-molecular-weight multimers, and therefore have reduced VWF activity which results in bleeding. Symptoms are typically more severe than those seen in type 1 VWD. Desmopressin may have clinical efficacy for treatment of minor bleeding, but significant surgical challenges or major bleeding symptoms generally require a VWF-containing concentrate for treatment.

Type 2B VWD results from gain-of-function mutations that increase the ability of VWF to bind platelets. This leads to increased clearance of both VWF and platelets from circulation and results in the loss of high-molecular-weight multimers and decreased VWF activity, similar to that seen in type 2A VWD. Special testing is, therefore, required to diagnose type 2B VWD, either by direct measurement of the increased platelet binding or by an increased response to low-dose ristocetin on platelet aggregation testing. Thrombocytopenia is not always present and may be more prominent during times of stress such as surgery or pregnancy. Desmopressin is relatively contraindicated in type 2B VWD as it may accelerate VWF-platelet binding and clearance.

Platelet-type, pseudo-VWD occurs when a mutation in platelet GPIb causes spontaneous binding to VWF and also presents with decreased VWF activity, loss of high-molecular-weight multimers, and thrombocytopenia similar to type 2B VWD. Specific testing is required to distinguish the 2 conditions. Because the defect involves platelets, treatment generally requires platelet transfusion.

Type 2M VWD includes those patients with decreased VWF activity but normal (or near-normal) multimer distribution. This is generally caused by a defect in the ability of VWF to bind platelet GPIb, but this category also includes patients with defects in VWF-collagen interactions. Some minor bleeding in type 2M VWD may respond to desmopressin, but because type 2M VWD is a functional defect, treatment with VWF-containing concentrates is usually required.

Type 2N VWD is characterized by a defect in VWF multimerization and decreased VWF activity in terms of platelet binding. It is the most common of the type 2 variants, accounting for approximately 10% of VWD cases. Type 2A VWD can result from mutations that affect multimer assembly and processing, or mutations that result in increased proteolysis of secreted VWF. Some mutations affect both secretion and clearance of the VWF. Regardless of the mechanism, all type 2A VWD patients lack the high-molecular-weight multimers, and therefore have reduced VWF activity which results in bleeding. Symptoms are typically more severe than those seen in type 1 VWD. Desmopressin may have clinical efficacy for treatment of minor bleeding, but significant surgical challenges or major bleeding symptoms generally require a VWF-containing concentrate for treatment.

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Type 2N VWD is characterized by a defect in VWF multimerization and decreased VWF activity in terms of platelet binding. It is the most common of the type 2 variants, accounting for approximately 10% of VWD cases. Type 2A VWD can result from mutations that affect multimer assembly and processing, or mutations that result in increased proteolysis of secreted VWF. Some mutations affect both secretion and clearance of the VWF. Regardless of the mechanism, all type 2A VWD patients lack the high-molecular-weight multimers, and therefore have reduced VWF activity which results in bleeding. Symptoms are typically more severe than those seen in type 1 VWD. Desmopressin may have clinical efficacy for treatment of minor bleeding, but significant surgical challenges or major bleeding symptoms generally require a VWF-containing concentrate for treatment.

**LABORATORY DIAGNOSIS**

There are no reliable screening tests for VWD. Patients with significant bleeding may present with anemia, and some patients with type 2B VWD or platelet-type, pseudo-VWD may have thrombocytopenia. The partial thromboplastin time may be prolonged if FVIII is low, but especially in mild type 1 VWD it is often normal, precluding use of the partial thromboplastin time as a screening test. Platelet function analysis has been considered as a screening test for VWD, but suboptimal
sensitivity and specificity render results difficult to interpret. Bleeding times are similarly unreliable in diagnosis of VWD.

Unfortunately there is no single test that can reliably diagnose VWD. Therefore a panel of tests is usually required. Table 477-1 lists the laboratory tests commonly used in diagnosis of VWD. These include VWF antigen (VWF:Ag), which measures the total amount of VWF protein present, and VWF activity, which is typically performed using the ristocetin cofactor activity assay (VWF:RCo) and provides a measure of the amount of functional VWF. FVIII activity is also usually included in the workup. Another important test is the VWF multimer distribution, although this is not routinely performed by all laboratories. Table 477-2 summarizes the expected laboratory findings for each type of VWD. Figure 477-1 provides more detailed analysis.

Additional specialized testing may be employed to help ascertain the correct diagnosis. Specific testing for type 1C (clearance defects), type 2B, and type 2N VWD can confirm these diagnoses. Genetic diagnosis is not typically performed, partly as a result of the large size of the VWF gene and the large number of benign sequence variations. Large gene deletions are responsible for some cases of VWD and will not be picked up on routine DNA sequencing. Use of genetic diagnosis is increasing, however, particularly for types 2A, 2B, 2M, and 2N VWD.

**TREATMENT**

Treatment of VWD depends on the type of VWD present and on the reason for treatment. Table 477-3 outlines the options for treatment. In general, type 1 VWD patients may be treated with desmopressin, which increases the amount of circulating VWF by release from storage. The exceptions are the rare type 1 patient who lacks a response to desmopressin, and patients with type 1C VWD who do respond with an increase in VWF levels, but whose rapid clearance of circulating VWF results in a rapid return to baseline levels. Treatment of types 2 and 3 VWD requires VWF-containing concentrates similar to the treatment of hemophilia. Dosing depends on the type of VWD, and reason for treatment. Careful monitoring of VWF and FVIII levels is recommended to tailor treatment for surgeries and major trauma. For all types of VWD, adjunct therapy should be
considered when possible, such as the use of antifibrinolytics for oral surgery or hormonal treatment for menorrhagia.

Alternate treatment strategies should also be considered, particularly for difficult symptoms or severe VWD. Hormonal therapy for women with menorrhagia, although not specific to VWD, can be very helpful in managing symptoms and improving quality of life. Local treatment of epistaxis, such as nasal cautery or packing, may be helpful in some circumstances. Iron therapy for patients with iron-deficiency anemia may also be required.

*Bibliography is available at Expert Consult.*

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**Table 477-2**  
VWD Classification

<table>
<thead>
<tr>
<th>VWF:Ag</th>
<th>VWF:RCo</th>
<th>FVIII</th>
<th>Multimer distribution</th>
<th>Type 1</th>
<th>Type 3</th>
<th>Type 2A</th>
<th>Type 2B*</th>
<th>Type 2M</th>
<th>Type 2N</th>
</tr>
</thead>
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<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Normal or ↓</td>
<td>Absent</td>
<td>↓↓</td>
<td>↓↓</td>
<td>Normal or ↓</td>
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</tr>
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<td>↓</td>
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<td>Normal or ↓</td>
<td>↓↓</td>
<td>Normal or ↓</td>
<td>Absent</td>
<td>↓↓</td>
<td>↓↓</td>
<td>Normal or ↓</td>
<td>↓</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal or ↓</td>
<td>Normal or ↓</td>
<td>↓↓</td>
<td>Normal or ↓</td>
<td>Absent</td>
<td>Loss of HMWM</td>
<td>Loss of HMWM</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Platelet count is also usually decreased in type 2B VWD.

FVIII, factor VIII; HMWM, high-molecular-weight multimers; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor activity.

**Table 477-3**  
VWD Treatment

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>VWD TYPES</th>
<th>ADMINISTRATION</th>
<th>DOsing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmopressin*</td>
<td>Type 1 VWD</td>
<td>IV or IN</td>
<td>0.3 μg/kg IV†</td>
</tr>
<tr>
<td></td>
<td>Some type 2 VWD (use with caution)</td>
<td></td>
<td>1 spray IN (&lt;50 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 sprays IN (&gt;50 kg)</td>
</tr>
<tr>
<td>von Willebrand factor concentrates¹</td>
<td>Type 3 VWD</td>
<td>IV</td>
<td>40-60 ristocetin cofactor activity units/kg (adjust dose depending on baseline VWF level and desired peak VWF level)</td>
</tr>
<tr>
<td></td>
<td>Type 2 VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe type 1 VWD (or type 1 clearance defects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifibrinolytics</td>
<td>Mucosal bleeding, all types of VWD</td>
<td>PO or IV</td>
<td>Aminocaproic acid: 100 mg/kg PO loading dose followed by 50 mg/kg q 6 hours§</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tranexamic acid: 1300 mg PO tid x 5 days</td>
</tr>
</tbody>
</table>

*Recommended treatment with Stimate brand nasal spray, as this form is concentrated to give 150 μg/spray. Other forms are much more dilute and will not result in desired increase in VWF.

†Maximum recommended dose is 20-30 μg/day.

¹Currently both Humate-P and Wilate are approved for treatment of VWD. A recombinant VWF preparation is currently undergoing clinical trials.

§Maximum recommended dose is 24 g/day.

IN, intranasal; IV, intravenous; PO, oral administration.
Bibliography


Pediatricians are frequently asked to evaluate children for inherited risk factors for thrombosis with symptomatic thrombosis or asymptomatic children who have relatives affected with either thrombosis or thrombophilia. The clinical utility of thrombophilia testing is debated, both in adults and children.

Thrombophilia testing rarely influences the acute management of a child with a thrombotic event. The association between inherited thrombophilia and pediatric thrombosis varies based on the clinical scenario: children with unprovoked thrombotic events have a high prevalence of inherited defects, while the role of thrombophilic defects in children with catheter-related thrombotic events is questionable. Although some thrombophilic defects are associated with a higher risk of recurrent venous thromboembolism in children, how to use these results to guide the duration of therapy has not been determined. Prospective longitudinal analyses of such patients to determine outcome and response to treatment as well as the impact of known thrombophilic states on these outcomes are clearly needed.

Pediatricians are frequently asked to evaluate children for inherited risk factors for thrombosis with symptomatic thrombosis or asymptomatic children who have relatives affected with either thrombosis or thrombophilia. The clinical utility of thrombophilia testing is debated, both in adults and children.

Table 478-1 lists the most common inherited thrombophilias and their prevalence in the general population. The inherited defects in which the pathogenic link is best understood include the factor V Leiden mutation, the prothrombin gene mutation, and deficiencies of
protein C, protein S, and antithrombin (AT). Elevated levels of factor VIII and homocysteine are associated with thrombosis, though these are less-well characterized and not necessarily genetically determined. Although there are additional alterations in coagulation that have been associated with thrombotic risk, including elevated concentrations of factors IX and XI, hepatic cofactor II deficiency, elevated lipoprotein (a), and dysfibrinogenemia, none has gained widespread acceptance in routine testing of children for inherited thrombophilia.

The factor V Leiden mutation is the result of a single nucleotide change at nucleotide 1765 within the factor V gene. This mutation causes factor Va to become resistant to inactivation by activated protein C and is the most common inherited risk factor for thrombosis. This defect is also known as activated protein C resistance. Approximately 5% of the U.S. white population is heterozygous for this mutation, and it is less prevalent in other ethnic groups. Individuals who are heterozygous have a 5–7-fold increase in risk of venous thrombosis, while homozygotes have a relative risk of 80–100. The baseline annual risk of thrombosis for young women of reproductive age is 1 per 12,500 and increases to 1 per 3,500 for those on oral contraceptives. For young women who are heterozygous for the factor V Leiden mutation and are taking oral contraceptives, this baseline annual risk is increased 20–30-fold (relative risk) to approximately 1 per 500 women.

The prothrombin 20210 gene mutation is a G-to-A transition in the 3’ untranslated region of the gene that results in increased levels of prothrombin messenger RNA. This variant is present in approximately 2% of U.S. whites. It is a weaker risk factor for venous thrombosis than factor V Leiden, with a relative risk of 2-3.

Deficiencies of protein C, protein S, and AT, the natural anticoagulant proteins, are more rare than the common genetic mutations described previously but are associated with a stronger risk of thrombosis. Although heterozygous deficiencies do not often present during childhood, homozygous defects may result in significant symptoms in infancy. Neonates with homozygous deficiencies of AT, protein C, or protein S may present with purpuric fulminans. This condition is characterized by rapidly spreading purpuric skin lesions resulting from thromboses of the small dermal vessels followed by bleeding into the skin. In addition, these infants may also develop cerebral thrombosis, ophthalmic thrombosis, disseminated intravascular coagulation, and large vessel thrombosis. An infant with purpuric skin lesions of unknown cause should receive initial replacement with fresh-frozen plasma. Definitive diagnosis can be difficult in the sick premature neonate who may have undetectable levels of these factors but not have a true genetic deficiency. Protein C and AT concentrations are also available and have been demonstrated to be effective.

Both venous and arterial thromboses are common in young patients with homocystinuria, an inborn error of metabolism caused by deficiency of cystathionine β-synthase. In this very rare condition, plasma levels of homocysteine exceed 100 μmol/L. Much more common are mild to moderate elevations of homocysteine, which may be acquired or associated with a polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene. Although moderate elevations of homocysteine have been associated with both venous and arterial thrombotic events, testing for polymorphisms in the MTHFR gene are not indicated, because these polymorphisms are not associated with venous thromboembolism. The pathogenic mechanisms for thrombosis in homocystinemia are not well understood.

Increased plasma concentrations of factor VIII (≥150 IU/dL) appear to be regulated by both genetic and environmental factors and are associated with an increased risk of thrombosis. Although there is a strong component of heritability contributing to factor VIII levels, the molecular mechanisms responsible for elevated factor VIII are not well understood. Factor VIII is also considered to be an acute-phase reactant, and may increase transiently during periods of inflammation.

Although interpretation of genetic studies (Factor V Leiden and Prothrombin gene mutations) are fairly straightforward, there are several challenges in interpretation of thrombophilia studies that are unique to pediatric patients. Neonates have decreased concentrations of protein C, protein S, and AT that increase rapidly over the first 6 mo of life; protein C concentrations remain below adult levels throughout much of childhood. It is important to use pediatric normal ranges when evaluating these values, and recognize that often the normal range overlaps with heterozygous defects and retesting may be required, particularly in young children. There are several nongenetic factors that may also influence the results of inherited thrombophilia testing, including acute thrombosis, infection, inflammation, hepatic dysfunction, nephrotic syndrome, medication and vitamin K deficiency. In some cases, the hereditary nature may be confirmed by testing the parents.

*Bibliography is available at Expert Consult.*
Bibliography
Compared to adults, children are generally protected from venous and arterial thromboses. Advancements in the treatment and supportive care of critically ill children, coupled with a heightened awareness of genetic risk factors for thrombosis, have led to an increase in the diagnosis of thromboembolic events (TEs) in children. As a result, TEs are not infrequent in pediatric tertiary care centers and may result in significant acute and chronic morbidity. Despite the fact that TEs in children are increasing in relative terms, they are still rare. This rarity has been the major impediment to prospective clinical trials, resulting in a deficit of evidence-based medicine. Diagnosis and treatment is often extrapolated from adult data.

**Epidemiology**

Studies have confirmed a significant increase in the diagnosis of venous thromboembolism (VTE) in pediatric tertiary hospitals across the United States. Although the overall incidence of thrombosis in the general pediatric population is quite low (0.07/100,000), the rate of VTE in hospitalized children is 60/10,000 admissions. Infants <1 yr old account for the largest proportion of pediatric VTEs, with a second peak during adolescence.

The majority of children who develop a TE have multiple risk factors that may be acquired, inherited, and/or anatomic (Table 479-1). The presence of a central venous catheter (CVC and peripherally inserted central venous catheter) is the single most important risk factor for VTE in pediatric patients, associated with approximately 90% of neonatal VTE and 60% of childhood VTE. These catheters are often necessary for the care of premature neonates and children with acute and chronic diseases and are used for intravenous hyperalimentation, chemotherapy, dialysis, antibiotics, or supportive therapy. CVCs may damage the endothelial lining and/or cause blood flow disruption, increasing the risk of thrombosis. There are multiple other acquired risk factors that are associated with thrombosis, including trauma, infection, chronic medical illnesses, and medications. Cancer, congenital heart disease, and prematurity are the most common medical conditions associated with TEs.

Antiphospholipid antibody syndrome (APS) is a well-described syndrome in adults characterized by recurrent fetal loss and/or thrombosis. Antiphospholipid antibodies are associated with both venous and arterial thrombosis. The mechanism by which these antibodies cause thrombosis is not well understood. A diagnosis of APS requires the presence of both clinical and laboratory abnormalities (see “Laboratory Testing” below). The laboratory abnormalities must be persistent for 12 wk. Because of the high risk of recurrence, patients with APS often require long-term anticoagulation. It is important to note that healthy children may have a transient lupus anticoagulant, often diagnosed because of a prolonged partial thromboplastin time on routine preoperative testing. These antibodies may be associated with a recent viral infection and are not a risk factor for thrombosis.

Anatomic abnormalities that impede blood flow also predispose patients to thrombosis at an earlier age. Atresia of the inferior vena cava has been described in association with acute and chronic lower extremity deep venous thrombosis (DVT). May-Thurner syndrome (compression of the left iliac vein by the overlying right iliac artery) should be considered in patients who present spontaneously with left iliofemoral thrombosis, and thoracic outlet obstruction (Paget-

**Clinical Manifestations**

**Extremity Deep Vein Thrombosis**

Children with acute DVT often present with extremity pain, swelling, and discoloration. A history of a current or recent CVC in that extremity should be very suggestive. Many times, symptoms of CVC-associated thrombosis are more subtle and chronic, including repeated CVC occlusion or sepsis, or prominent venous collaterals on the chest, face, and neck.

**Pulmonary Embolism**

Symptoms of pulmonary embolism (PE) include shortness of breath, pleuritic chest pain, cough, hemoptysis, fever, and, in the case of massive PE, hypotension and right-heart failure. Based on autopsy studies, PE is often not diagnosed, perhaps because young children are unable to accurately describe their symptoms and their respiratory deterioration may be masked by other conditions (see Chapter 407.1).

**Cerebral Sinovenous Thrombosis**

Symptoms may be subtle and may develop over many hours or days. Neonates often present with seizures, whereas older children often complain of headache, vomiting, seizures, and focal signs. They may also have papilledema and abducens palsy. Some patients may have a concurrent sinusitis or mastoiditis that has contributed to the thrombosis.

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**Table 479-1 Risk Factors for Thrombosis**

<table>
<thead>
<tr>
<th>General</th>
<th>Inherited thrombophilia</th>
<th>Anatomic</th>
<th>Medications</th>
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</thead>
<tbody>
<tr>
<td>Indwelling catheter including PICC (peripherally inserted central venous catheter) lines</td>
<td>Factor V Leiden mutation</td>
<td>Thoracic outlet obstruction (Paget-Schroetter syndrome)</td>
<td>Estrogen-containing contraceptives</td>
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<td>Infection</td>
<td>Prothrombin mutation</td>
<td>May-Thurner syndrome</td>
<td>Asparaginase</td>
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<td>Trauma</td>
<td>Antithrombin deficiency</td>
<td>Absence of the inferior vena cava</td>
<td>Heparin (heparin-induced thrombocytopenia)</td>
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<td>Protein C deficiency</td>
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<td>Protein S deficiency</td>
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<td>Prematurity</td>
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<td>Paroxysmal nocturnal hemoglobinuria</td>
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<tr>
<td>Thrombotic thrombocytopenic purpura</td>
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</table>

**Schroetter syndrome** frequently presents with effort-related axillary-subclavian vein thrombosis.
Renal Vein Thrombosis
Renal vein thrombosis is the most common spontaneous TE in neonates. Affected infants may present with hematuria, an abdominal mass, and/or thrombocytopenia. Infants of diabetic mothers are at increased risk, although the mechanism for this increased risk is unknown. Approximately 25% of cases are bilateral.

Peripheral Arterial Thrombosis
With the exception of stroke, the majority of arterial TEs in children are secondary to catheters, often in neonates related to umbilical artery lines or in patients with cardiac defects undergoing cardiac catheterization. Patients with an arterial thrombosis affecting blood flow to an extremity will present with a cold, pale, blue extremity with poor or absent pulses.

Stroke
Ischemic stroke commonly presents with hemiparesis, loss of consciousness, or seizures. This condition may occur secondary to pathology that affects the intracranial arteries (e.g., sickle cell disease, vasculopathy, or traumatic arterial dissection) or may be a result of venous thrombi that embolize to the arterial circulation (placental thrombi, children with congenital heart disease or patent foramen ovale).

Rapidly Progressive Thrombosis/Thrombotic Storm
Rapid progression or multifocal thrombosis is a rare complication of the APS, heparin-induced thrombocytopenia with thrombosis or thrombotic thrombocytopenia purpura while on appropriate antithrombotic therapy. Multiple organ dysfunctions develop in the presence of small vessel occlusion and elevated D-dimer levels. Recurrences may occur as well as postthrombotic syndrome (PTS). Treatment includes aggressive anticoagulation, often with direct thrombin inhibitors or fondaparinux followed by prolonged warfarin therapy.

DIAGNOSIS
Ultrasound with Doppler flow is the most commonly employed imaging study for the diagnosis of upper, or more often lower, extremity VTE. Spiral CT is used most frequently for the diagnosis of PE (Fig. 479-1). Other diagnostic imaging options include CT and MR venography, which are noninvasive, although the sensitivity and specificity of these studies is not known. They may be particularly helpful in evaluating proximal thrombosis. For the diagnosis of cerebral sinus venous thrombosis and acute ischemic stroke, the most sensitive imaging study is brain magnetic resonance imaging with venography or diffusion weighted imaging.

LABORATORY TESTING
All children with a TE should have a complete blood count and a baseline prothrombin time (PT) and activated partial thromboplastin time (aPTT) to assess their coagulation status. In adults suspected to have a DVT, the D-dimer level has a high negative predictive value. The D-dimer is a fragment produced when fibrin is degraded by plasmin and is a measure of fibrinolysis. Based on the clinical scenario, other laboratory studies, such as renal and hepatic function, may be indicated. Testing for APS includes evaluation for the lupus anticoagulant as well as anticardiolipin and anti-β2-glycoprotein antibodies.

There is some debate regarding which patients should have testing for inherited risk factors. Thrombophilia testing rarely influences the acute management of a child with a thrombotic event. Identification of an inherited thrombophilia may influence the duration of treatment, particularly for those with combined defects, and may aid in counseling the patient about their risk of recurrence.

The evaluation of coagulation studies in pediatric patients is often complicated by the developing hematostatic system and the differences in normal ranges between infants and adults. In addition, there is often significant variation in the laboratory assays used to test anticoagulant levels. It is important to refer to the age-related normal ranges when interpreting pediatric coagulation studies. One limitation of these normal ranges is that they were performed many years ago, using assays that may not be equivalent to those used today. Molecular assays are not age dependent.

TREATMENT
Therapeutic options for children with thrombosis include anticoagulation, thrombolysis, surgery, and observation. The goal of anticoagulation is to reduce the risk of embolism, halt clot extension, and prevent recurrence. In premature neonates and critically ill children who may have an increased risk of bleeding, the potential benefits must be weighed against the risks. Anticoagulants and thrombolysis are discussed in greater detail in Chapter 479.1. Surgery may be necessary for life- or limb-threatening thrombosis when there is a contraindication to thrombolysis. The optimal treatment for a child with acute ischemic stroke depends on the likely etiology and the size of the infarct. Children with sickle cell disease who develop stroke are treated with chronic red blood cell transfusions to reduce recurrence.

COMPLICATIONS
Complications of VTE include recurrent thrombosis (either local or distant), and development of PTS. A thrombosed blood vessel may partially or fully recanalize or may remain occluded. Over time, an occluded deep vein may cause venous hypertension, resulting in blood flow being directed from the deep system into the superficial veins and potentially producing pain, swelling, edema, discoloration, and ulceration. This clinical picture is known as PTS and may be chronically disabling. Several prospective studies in adults have shown PTS to be present in 17-50% of patients with a history of thrombosis. The likelihood of developing PTS is highest in the first 2 yr but continues to increase over time.

479.1 Anticoagulant and Thrombolytic Therapy
Leslie J. Raffini and J. Paul Scott

Initial options for anticoagulation in children include unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) (Table 479-2). Although there are additional agents, including target specific oral anticoagulants, none have been carefully investigated in children. Both UFH and LMWH act by catalyzing the action of antithrombin (AT)-III. UFH consists of large-molecular-weight polysaccharide chains that interact with AT, catalyzing the inhibition of factor Xa and thrombin, as well as other serine proteases. In contrast, LMWH contains smaller-molecular-weight polysaccharide chains. The interaction of the smaller chains with AT-III results primarily in the inhibition of
There are several alternative parenteral anticoagulants (argatroban, enoxaparin). HIT is strongly suspected, heparin must be discontinued immediately.

Thrombocytopenia, and in some cases, life-threatening thrombosis. If antibodies develop to a complex of heparin and platelet factor 4. These antibodies result in platelet activation, stimulation of coagulation, thrombocytopenia, and in some cases, life-threatening thrombosis. If HIT is strongly suspected, heparin must be discontinued immediately.

There are several alternative parenteral anticoagulants (argatroban, lepirudin, or bivalirudin) that may be used in this situation.

Xa, with less of an effect on thrombin. There are several LMWHs available, and they have variable inhibitory effects on thrombin. For this reason, the PTT is not a reliable measure of the anticoagulant effect of LMWH, and the anti-factor Xa activity is used instead.

The optimal duration of anticoagulation for children with TEs is not well established. Current guidelines recommend that neonates receive 6 wk-3 mo of therapy for VTE, and older children receive 3-6 mo of therapy. Patients with strong inherited thrombophilia, recurrent thrombosis, and APS may require indefinite anticoagulation.

UNFRACTIONATED HEPARIN

Heparin Dosing

Based on adult data, a therapeutic heparin dose achieves a prolongation of the aPTT of 1.5-2.5 the upper limit of normal. A bolus dose of 75-100 units/kg results in a therapeutic PTT in the majority of children. This bolus should be followed by a continuous infusion. Initial dosing is based on age, with infants having the highest requirements. It is important to continue to monitor the PTT closely. In some situations, such as patients with a lupus anticoagulant, elevated factor VIII, or neonates, the partial thromboplastin time may not accurately reflect the degree of anticoagulation, and heparin can be monitored using a heparin anti-Xa level of 0.35-0.7 units/mL.

Heparin Complications

Maintaining the aPTT in the therapeutic range can be difficult in young children for several reasons. The bioavailability of heparin is difficult to predict and may be influenced by plasma proteins. In many patients, this results in multiple dose adjustments requiring close monitoring with frequent venipuncture. UFH also requires continuous intravenous access, which may be difficult to maintain in young children.

The most common adverse effect related to heparin therapy is bleeding. This is well documented in the adult medical literature, and there are case reports of serious life-threatening bleeding in children treated with heparin. The true frequency of bleeding in pediatric patients on heparin has not been well established and is reported as 1-24%. If the anticoagulant effect of heparin must be reversed immediately, protamine sulfate may be administered to neutralize the heparin.

Other adverse effects include osteoporosis and heparin-induced thrombocytopения (HIT). Although rare in pediatric populations, HIT is a prothrombotic, immune-mediated complication in which antibodies develop to a complex of heparin and platelet factor 4. These antibodies result in platelet activation, stimulation of coagulation, thrombocytopения, and in some cases, life-threatening thrombosis. If HIT is strongly suspected, heparin must be discontinued immediately.

There are several alternative parenteral anticoagulants (argatroban, lepirudin, or bivalirudin) that may be used in this situation.

LOW-MOLECULAR-WEIGHT HEPARIN

Because of the ease of dosing and need for less monitoring, LMWH is being used more frequently in pediatric patients. Unlike UFH, which is monitored using the aPTT, LMWH is monitored via the anti-Xa activity. The LMWH formulation that has been used most often in pediatric patients is enoxaparin.

Enoxaparin Dosing

The recommended standard starting dose of enoxaparin for infants <2 mo is 1.5 mg/kg/dose SQ every 12 hr; for patients >2 mo it is 1 mg/kg SQ every 12 hr. In general, peak levels are achieved 2-6 hr following an injection. A therapeutic anti-factor Xa level, drawn 4 hr after the 2nd or 3rd dose, should be between 0.5 and 1.0 IU/mL. The dose can be titrated to achieve this range. The elimination half-life of enoxaparin is 4-6 hr. Enoxaparin is cleared by the kidney and should be used with caution in patients with renal insufficiency. It should be avoided in patients with renal failure.

After an initial period of anticoagulation with heparin or LMWH, patients may continue to receive LMWH as an outpatient for the duration of therapy, or may be transitioned to an oral anticoagulant, such as warfarin.

WARFARIN

Warfarin is an oral anticoagulant that competitively interferes with vitamin K metabolism, exerting its action by decreasing concentrations of the vitamin K–dependent coagulation factors II, VII, IX, and X, as well as protein C and protein S. Therapy should be started while a patient is anticoagulated with heparin or LMWH because of the risk of warfarin-induced skin necrosis. This transient hypercoagulable condition may occur when levels of protein C drop more rapidly than the procoagulant factors.

Warfarin Dosing

Warfarin therapy is often initiated with a loading dose, with subsequent dose adjustments made according to a nomogram. When initiating a patient on warfarin, UFH or LMWH should be continued until the international normalized ratio (INR) is therapeutic for 2 days. In most cases, this takes 5-7 days. The PT is used to monitor the anticoagulant effect of warfarin. Because the thromboplastin reagents used in PT assays have widely varying sensitivities, it is not possible to compare the PT performed in one laboratory to that performed in another laboratory. As a result, the INR was developed as a mechanism to standardize the variation in the thromboplastin reagent. The target INR range depends on the clinical situation. In general, a range of 2.0-3.0 is the target for the treatment of VTE. High-risk patients, such as those with mechanical heart valves, APS, and recurrent thrombosis, may require a higher target range.

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Table 479-2 | Comparison of Antithrombotic Agents

<table>
<thead>
<tr>
<th>rTPA</th>
<th>UNFRACTIONATED HEPARIN*</th>
<th>WARFARIN</th>
<th>LMW HEPARIN (ENOXAPARIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Recent onset of life- or limb-threatening thrombus</td>
<td>Acute or chronic thrombus, prophylaxis</td>
<td>Subacute or chronic thrombosis, thromboprophylaxis for cardiac valves</td>
</tr>
<tr>
<td>Administration</td>
<td>IV, Continuous infusion</td>
<td>IV, Continuous infusion</td>
<td>PO, once daily</td>
</tr>
<tr>
<td>Monitoring</td>
<td>“Lytic state”: FDP or D-dimer</td>
<td>PTT</td>
<td>INR</td>
</tr>
<tr>
<td>Other</td>
<td>Higher risk of bleeding</td>
<td>Difficult to titrate, requires frequent dose adjustments</td>
<td>Heavily influenced by drug and diet</td>
</tr>
</tbody>
</table>

*Higher dose is required in newborns.

FDP, fibrin degradation product; INR, international normalized ratio; LMW, low-molecular-weight; PTT, partial thromboplastin time; rTPA, recombinant tissue-type plasminogen activator.
**Warfarin Complications**

As with the other anticoagulants, bleeding is the most common adverse effect. The risk of serious bleeding in children receiving warfarin for the treatment of VTE has been reported at 1.7%. Children who have supratherapeutic INRs are at higher risk. There is considerable inter-patient variation in dose. Diet, medications, and illness may influence the metabolism of warfarin, requiring frequent dose adjustments and laboratory studies. Numerous medications can affect the pharmacokinetics of warfarin by altering its clearance or rate of absorption. This can have a profound effect on the INR, and must be considered when monitoring a patient on warfarin.

The strategies used to reverse warfarin therapy depend on the clinical situation and whether or not there is bleeding. Vitamin K can be administered to reverse the effect of warfarin but takes some time to have effect. If the patient is having significant bleeding, fresh-frozen plasma (15 mL/kg) should be given along with the vitamin K.

Nonhemorrhagic complications are uncommon in children. Warfarin is a teratogen, particularly in the first trimester. Warfarin embryopathy is characterized by bone and cartilage abnormalities known as chondrodysplasia punctata. Affected infants may have nasal hypoplasia and excessive calcifications in the epiphyses and vertebralae.

**DIRECT THROMBIN OR FACTOR XA INHIBITORS**

Direct thrombin inhibitors (dabigatran) or inhibitors of factor Xa (apixaban, rivaroxaban) have been tested as agents to prevent or treat venous thrombosis in adult populations with increased risk of thrombosis (surgery, immobilization, atrial fibrillation). Fixed dosing, oral administration, no dietary interference with vitamin K, and no need to monitor laboratory tests, as well as initial results suggesting noninferiority to warfarin and fewer bleeding episodes, have favored the use of these agents. Currently there is a paucity of evidence of their utility in children.

**THROMBOLYTIC THERAPY**

Although anticoagulation alone is often effective at managing thrombosis, there are times when more rapid clot resolution is necessary or desirable. In these situations, thrombolytic agents that activate the fibrinolytic system are of potential benefit. The pharmacologic activity of thrombolytic agents is dependent on the conversion of endogenous plasminogen to plasmin. Plasmin is then able to degrade several plasma proteins including fibrin and fibrinogen. Because of the high risk of bleeding, thrombolytic therapy is generally reserved for patients with life or limb-threatening thrombosis.

**Tissue plasminogen activator** (TPA) is available as a recombinant product and has become the primary agent used for thrombolysis in children, although proper dose finding studies have not been performed in a pediatric population.

**Dosing**

There is an extremely wide range of doses of TPA that have been used for systemic therapy, and there is no consensus as to the optimal dose. Previously recommended doses of systemic TPA were 0.1-0.6 mg/kg/hr; however there are recent reports of successful therapy with fewer bleeding complications using prolonged infusions with very low doses—0.01-0.06 mg/kg/hr.

**Monitoring**

There is no specific laboratory test to document a “therapeutic range” for thrombolytic therapy. It is important to maintain the fibrinogen >100 mg/dL and the platelet count >75,000/mm$^3$ during treatment. Supplementation of plasminogen using fresh-frozen plasma is generally recommended in neonates prior to initiating thrombolysis because of their low baseline levels.

The clinical and radiologic response to thrombolysis should be closely monitored. The duration of therapy depends on the clinical response. Invasive procedures including urinary catheterization, arterial puncture and rectal temperatures should be avoided.

The role of adjuvant UFH during thrombolytic therapy is controversial. Animal models have demonstrated that thrombolytic therapy can induce a procoagulant state with activation of the coagulation system, generation of thrombin, and extension or reocclusion of the thrombus. In pediatric patients thought to be at low risk for bleeding, adjuvant UFH should be considered using doses of 10-20 units/kg/hr.

**Complications**

The most serious complication from thrombolysis is bleeding, which has been reported in 0-40% of patients. Absolute contraindications to thrombolysis include major surgery within 7 days, history of significant bleeding (intracranial, pulmonary or gastrointestinal), peripartum asphyxia with brain damage, uncontrolled hypertension and severe thrombocytopenia. In the event of serious bleeding, thrombolysis should be stopped and cryoprecipitate may be given to replace fibrinogen.

**THROMBOPROPHYLAXIS**

There have been no formal trials of prevention of venous thromboembolic disease in children. Hospitalized adolescents with multiple risk factors for thrombosis who are immobilized for a protracted time may benefit from prophylactic treatment with enoxaparin 0.5 mg/kg q12hr (maximum: 30 mg).

**ANTIPLATELET THERAPY**

Inhibition of platelet function using agents such as aspirin is more likely to be protective against arterial TEs than VTEs. Aspirin, also known as acetylsalicylic acid, exerts its antiplatelet effect by irreversibly inhibiting cyclooxygenase, preventing platelet thromboxane A$_2$ production. Aspirin is used routinely in children with Kawasaki disease and may also be useful in children with stroke, ventricular assist devices, and those with single-ventricle cardiac defects. The recommended dose of aspirin to achieve an antiplatelet effect in children is 1-5 mg/kg/day.

*Bibliography is available at Expert Consult.*
Although “late” hemorrhagic disease has been reported in breastfed children, vitamin K deficiency occurring after the neonatal period is usually secondary to a lack of oral intake of vitamin K, alterations in the gut flora as a consequence of the long-term use of broad-spectrum antibiotics, liver disease, or malabsorption of vitamin K. Intestinal malabsorption of fats may accompany cystic fibrosis or biliary atresia and result in a deficiency of fat-soluble dietary vitamins, with reduced synthesis of vitamin K–dependent clotting factors (factors II, VII, IX, and X, and proteins C and S). Prophylactic administration of water-soluble vitamin K orally is indicated in these cases (2-3 mg/24 hr for children and 5-10 mg/24 hr for adolescents and adults), or vitamin K may be administered at 1-2 mg IV. In patients with advanced cirrhosis, synthesis of many of the clotting factors may be reduced because of hepatocellular damage. In these patients, vitamin K may be ineffective. The anticoagulant properties of warfarin (Coumadin) and related anticoagulants depend on interference with vitamin K, with a concomitant reduction of factors II, VII, IX, and X. Rat poison (superwarfarin) produces a similar deficiency; vitamin K is a specific antidote.

_Bibliography is available at Expert Consult._
Bibliography


Because all of the clotting factors, except factor VIII, are produced exclusively in the liver, coagulation abnormalities are very common in patients with severe liver disease. Only 15% of such patients have significant clinical bleeding states. The severity of the coagulation abnormality appears to be directly proportional to the extent of hepatocellular damage. The most common mechanism causing the defect is decreased synthesis of coagulation factors. Patients with severe liver disease characteristically have normal to increased (not reduced) levels of factor VIII activity in plasma. In some instances, disseminated intravascular coagulation (see Chapter 483) or hyperfibrinolysis may complicate liver disease, making laboratory differentiation of severe liver disease from disseminated intravascular coagulation difficult.

Treatment of the coagulopathy of liver disease should be reserved for patients with clinical bleeding. Because a reduction in vitamin K-dependent coagulation factors is common in those with acute or chronic liver disease, vitamin K therapy can be given as a trial. Vitamin K can be given orally, subcutaneously, or intravenously (not intramuscularly) at a dose of 1 mg/24 hr for infants, 2-3 mg/24 hr for children, and 5-10 mg/24 hr for adolescents and adults. Inability to correct coagulopathy with vitamin K indicates that the coagulopathy may be caused by reduced levels of clotting factors that are not vitamin K-dependent and/or by inadequate production of precursor vitamin K proteins. Treatment for bleeding consists of factor replacement with fresh-frozen plasma (FFP) or cryoprecipitate. FFP (10-15 mL/kg) contains all clotting factors, but replacement of fibrinogen for severe hypofibrinogenemia may require cryoprecipitate at a dose of 1 bag/5 kg body weight. In severe liver disease, it is often difficult to attain correction of abnormal clotting studies despite vigorous therapy with FFP and cryoprecipitate. Some patients with bleeding as a result of liver disease have responded to therapy with desmopressin, and others have responded to treatment with recombinant factor VIIa.

Frequently, severe liver disease is associated with moderate prolongation of bleeding time that is not corrected by either vitamin K or plasma replacement. Desmopressin (0.3 µg/kg IV) is effective in shortening bleeding time and is used effectively to augment hemostasis before liver biopsy. In clinical trials of adults, recombinant factor VIIa has not been shown to be effective for the treatment of bleeding caused by severe liver disease.

Bibliography is available at Expert Consult.
Bibliography

Acquired circulating anticoagulants (inhibitors) are antibodies that react or crossreact with clotting factors or components used in coagulation screening tests (phospholipids), thereby prolonging screening tests, such as prothrombin time and partial thromboplastin time. Some of these anticoagulants are autoantibodies that react with phospholipid and thereby interfere with clotting in vitro but not in vivo. The most common form of these antiphospholipid antibodies has been referred to as the lupus anticoagulant (see Chapter 476.1). This anticoagulant is found in patients with systemic lupus erythematosus (see Chapter 158), in those with other collagen-vascular diseases, and in association with HIV. In otherwise healthy children, spontaneous lupus-like inhibitors have developed transiently after incidental viral infection. These transient inhibitors are usually not associated with either bleeding or thrombosis.

Although the classic lupus anticoagulant is more often associated with a predisposition to thrombosis than with bleeding symptoms, bleeding symptoms in a patient with the lupus anticoagulant may be caused by thrombocytopenia, as a manifestation of the antiphospholipid syndrome or of lupus itself, or, rarely, by a coexistent specific autoantibody against prothrombin (factor II). This antiprothrombin antibody does not inactivate prothrombin, but causes accelerated clearance of the protein, resulting in low levels of prothrombin.

Rarely, antibodies may arise spontaneously against a specific clotting factor, such as factor VIII or von Willebrand factor, similar to those seen more frequently in elderly patients. These patients are prone to excessive hemorrhage and may require specific treatment. In patients with a hereditary deficiency of a clotting factor (factor VIII or factor IX), antibodies may develop after exposure to transfused factor concentrates. These hemophilic inhibitory antibodies are discussed in Chapter 479.1.

**LABORATORY FINDINGS**

Inhibitors against specific coagulation factors usually affect factors VIII, IX, and XI, or, rarely, prothrombin. Depending on the target of the antibody, prothrombin time, partial thromboplastin time, or both may be prolonged. The mechanism by which the inhibitory antibody functions determines whether mixing patient plasma with normal plasma will normalize (correct) the clotting time. Patient plasma containing antibodies directed against the active site of the clotting factor (factor VIII or factor IX) will not correct on 1:1 mixing with normal plasma, whereas antibodies that lead to increased clearance of the factor (prothrombin) will correct on 1:1 mixing. Specific factor assays are used to determine which factor is involved.

**TREATMENT**

Management of the bleeding patient with an inhibitor against factor VIII or IX is the same as for the patient with hemophilia who has an alloantibody against factor VIII or factor IX. Infusions of recombinant factor VIIIa or activated prothrombin complex concentrate may be needed to control significant bleeding. Immunosuppressive agents have used off-label to treat the inhibitor or reduce titers. Acute bleeding caused by an antiprothrombin antibody can often be treated with a plasma infusion and may benefit from a short course of corticosteroid therapy.

Asymptomatic spontaneous inhibitors that arise after a viral infection tend to disappear within a few weeks to months. Inhibitors seen with an underlying disease, such as systemic lupus erythematosus, often disappear when the primary disease is effectively treated.

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Bibliography


Thrombotic microangiopathy refers to a heterogeneous group of conditions, including disseminated intravascular coagulation (DIC), that result in consumption of clotting factors, platelets, and anticoagulant proteins. Consequences of this process include widespread intravascular deposition of fibrin, leading to tissue ischemia and necrosis, a generalized hemorrhagic state, and hemolytic anemia.

**ETIOLOGY**
Any life-threatening severe systemic disease (Table 483-1) associated with hypoxia, acidosis, tissue necrosis, shock, and/or endothelial damage may trigger DIC. Better understanding of the pathophysiology of hemostasis has lead to an appreciation of the critical interaction of the coagulation pathways with the innate immune system and inflammatory response that likely contributes to the widespread dysregulation present in DIC. Activation and release of cytokines and chemokines alter endothelial function to a more prothrombotic state, enhancing the formation of microvascular thromboses, with resultant consumption of pro- and anticoagulant proteins. Excessive activation of clotting consumes both the physiologic anticoagulants (protein C, protein S, and antithrombin III) and procoagulants, resulting in a deficiency of factor V, factor VIII, prothrombin, fibrinogen, and platelets. Commonly, the clinical result of this sequence of events is hemorrhage. The hemostatic dysregulation may also result in thromboses in the skin, kidneys, and other organs.

**CLINICAL MANIFESTATIONS**
DIC accompanies a severe systemic disease process, usually with shock. Bleeding frequently first occurs from sites of venipuncture or surgical incision. The skin may show petechiae and ecchymoses. Tissue necrosis may involve many organs and can be most spectacularly seen as infarction of large areas of skin, subcutaneous tissue, or kidneys. Anemia caused by hemolysis may develop rapidly, owing to microangiopathic hemolytic anemia.

**LABORATORY FINDINGS**
There is no well-defined sequence of events. Certain coagulation factors (factors II, V, and VIII, and fibrinogen) and platelets may be consumed by the ongoing intravascular clotting process, with resultant prolongation of the prothrombin, partial thromboplastin, and thrombin times. Platelet counts may be profoundly depressed. The blood smear may contain fragmented, Burr- and helmet-shaped red blood cells (schistocytes). In addition, because the fibrinolytic mechanism is activated, fibrinogen degradation products (D-dimers) appear in the blood. The D-dimer is formed by fibrinolysis of a crosslinked fibrin clot. The D-dimer assay is as sensitive as the fibrinogen degradation product test and more specific for activation of coagulation and fibrinolysis.

**TREATMENT**
The first 2 steps in the treatment of DIC are the most critical: (a) treat the trigger that caused DIC and (b) restore normal homeostasis by correcting the shock, acidosis, and hypoxia that usually complicate DIC. If the underlying problem can be controlled and the patient stabilized, bleeding quickly ceases, and there is improvement of the abnormal laboratory findings. Blood components are used for replacement therapy in patients with hemorrhage and may consist of platelet infusions (for thrombocytopenia), cryoprecipitate (for hypofibrinogenemia), and/or fresh-frozen plasma (for replacement of other coagulation factors and natural inhibitors).

The role of heparin in DIC is limited to patients who have vascular thrombosis in association with DIC or who require prophylaxis because they are at high risk for venous thromboembolism. Such individuals should be treated as outlined in Chapter 479, with careful attention to replacement therapy to maintain an adequate platelet count and thus limit bleeding complications.

**Table 483-1 Causes of Disseminated Intravascular Coagulation**

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes of DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTIOUS</td>
<td>Meningococcemia (purpura fulminans)</td>
</tr>
<tr>
<td></td>
<td>Bacterial sepsis (staphylococcal, streptococcal, Escherichia coli, Salmonella)</td>
</tr>
<tr>
<td></td>
<td>Rickeitsia (Rocky Mountain spotted fever)</td>
</tr>
<tr>
<td></td>
<td>Virus (cytomegalovirus, herpes simplex, hemorrhagic fevers)</td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
</tr>
<tr>
<td></td>
<td>Fungus</td>
</tr>
<tr>
<td>TISSUE INJURY</td>
<td>Central nervous system trauma (massive head injury)</td>
</tr>
<tr>
<td></td>
<td>Multiple fractures with fat emboli</td>
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<tr>
<td></td>
<td>Crush injury</td>
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<tr>
<td></td>
<td>Profound shock or asphyxia</td>
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<td></td>
<td>Hypothermia or hyperthermia</td>
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<td></td>
<td>Massive burns</td>
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<tr>
<td>MALIGNANCY</td>
<td>Acute promyelocytic leukemia</td>
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<tr>
<td></td>
<td>Acute monoblastic or promyelocytic leukemia</td>
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<tr>
<td></td>
<td>Widespread malignancies (neuroblastoma)</td>
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<tr>
<td>VENOM OR TOXIN</td>
<td>Snake bites</td>
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<tr>
<td></td>
<td>Insect bites</td>
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<tr>
<td>MICROANGIOPATHIC DISORDERS</td>
<td>“Severe” thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome</td>
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<tr>
<td></td>
<td>Giant hemangioma (Kasabach-Merritt syndrome)</td>
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<td>GASTROINTESTINAL DISORDERS</td>
<td>Fulminant hepatitis</td>
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<td>Ischemic bowel</td>
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<tr>
<td></td>
<td>Pancreatitis</td>
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<tr>
<td>HEREDITARY THROMBOTIC DISORDERS</td>
<td>Antithrombin III deficiency</td>
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<td>Homozygous protein C deficiency</td>
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<td>NEWBORN</td>
<td>Maternal toxemia</td>
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<td>Bacterial or viral sepsis (group B streptococcus, herpes simplex)</td>
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<td>Abruptio placenta</td>
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<td>Severe respiratory distress syndrome</td>
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<td></td>
<td>Necrotizing enterocolitis</td>
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<td></td>
<td>Erythroblastosis fetalis</td>
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<td></td>
<td>Fetal demise of a twin</td>
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<td>MISCELLANEOUS</td>
<td>Severe acute graft rejection</td>
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<td></td>
<td>Acute hemolytic transfusion reaction</td>
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<td></td>
<td>Severe collagen-vascular disease</td>
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<td>Kawasaki disease</td>
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<td>Heparin-induced thrombosis</td>
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<td></td>
<td>Infusion of “activated” prothrombin complex concentrates</td>
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<td></td>
<td>Hyperpyrexia/encephalopathy, hemorrhagic shock syndrome</td>
</tr>
</tbody>
</table>

The prognosis of patients with DIC is primarily dependent on the outcome of the treatment of the primary disease and prevention of end-organ damage.

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Bibliography

MEGAKARYOPOIESIS
Platelets are nonnucleated cellular fragments produced by megakaryocytes within the bone marrow and other tissues. Megakaryocytes are large polyploid cells. When the megakaryocyte approaches maturity, budding of the cytoplasm occurs and large numbers of platelets are liberated. Platelets circulate with a life span of 10-14 days. Thrombopoietin (TPO) is the primary growth factor that controls platelet production (Fig. 484-1). Levels of TPO appear to correlate inversely with platelet number and megakaryocyte mass. Levels of TPO are highest in the thrombocytopenic states associated with decreased marrow megakaryopoiesis and may be variable in states of increased platelet production.

The platelet plays multiple hemostatic roles. The platelet surface possesses a number of important receptors for adhesive proteins, including von Willebrand factor (VWF) and fibrinogen, as well as receptors for agonists that trigger platelet aggregation, such as thrombin, collagen, and adenosine diphosphate (ADP). After injury to the blood vessel wall, the extracellular matrix containing adhesive and procoagulant proteins is exposed. Subendothelial collagen binds VWF. VWF undergoes a conformational change that induces binding of the platelet glycoprotein Ib (GPIb) complex, the VWF receptor. This process is called platelet adhesion. Platelets then undergo activation. During the process of activation, the platelets generate thromboxane A₂ from arachidonic acid via the enzyme cyclooxygenase. After activation, platelets release agonists, such as ADP, adenosine triphosphate (ATP), Ca²⁺, serotonin, and coagulation factors, into the surrounding milieu. Binding of VWF to the GPIb complex triggers a complex signaling cascade that results in activation of the fibrinogen receptor, the major platelet integrin glycoprotein αIIb-β₃ (GPIIb-IIIa). Circulating fibrinogen binds to its receptor on the activated platelets, complex linking platelets together in a process called aggregation. This series of events forms a hemostatic plug at the site of vascular injury. The serotonin and histamine that are liberated during activation increase local vasoconstriction. In addition to acting in concert with the vessel wall to form the platelet plug, the platelet provides the catalytic surface on which coagulation factors assemble and eventually generate thrombin through a sequential series of enzymatic cleavages. Last, the platelet contractile proteins and cytoskeleton mediate clot retraction.

THROMBOCYTOPENIA
The normal platelet count is 150-450 × 10⁹/L. Thrombocytopenia refers to a reduction in platelet count to <150 × 10⁹/L. Causes of thrombocytopenia include decreased production on either a congenital or an acquired basis, sequestration of the platelets within an enlarged spleen or other organ, and increased destruction of normally synthesized platelets on either an immune or a nonimmune basis (see Chapter 475; Tables 484-1 and 484-2 and Fig. 484-2).

Figure 484-1 Scheme of megakaryocytopenesis and platelet production in idiopathic thrombocytopenic purpura. Hematopoietic stem cells (HSC) are mobilized and megakaryocyte (MK) and erythroid progenitors (MEP) accumulate with MK-committed progenitors (MKP) giving rise to mature MKs under control of thrombopoietin (TPO) working with chemokines, cytokines, and growth factors, including stem cell factor (SCF) and interleukin (IL)-3, IL-6, and IL-11. Endoreplication in ploidy changes in MKs and increased chromosome number (up to 64N). Mature MKs migrate to the endothelial cell barrier delimiting the vascular sinus and, under the influence of stromal-derived factor-1 (SDF-1), give rise to proplatelets that protrude into the circulation and produce large numbers of platelets under hemodynamic determinants. Therapeutically given romiplostim and eltrombopag enter the marrow and join with TPO to stimulate megakaryocytopenesis and platelet production. (From Nurden AT, Viallard JF, Nurden P: New-generation drugs that stimulate platelet production in chronic immune thrombocytopenic purpura, Lancet 373:1562–1568, 2009, p. 1563.)
Bibliography


Table 484-1  Differential Diagnosis of Thrombocytopenia in Children and Adolescents

<table>
<thead>
<tr>
<th>Destructive Thrombocytopenias</th>
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<tbody>
<tr>
<td>Primary Platelet Consumption Syndromes</td>
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<tr>
<td>Immune thrombocytopenias</td>
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<tr>
<td>Acute and chronic ITP</td>
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<td>Autoimmune diseases with chronic ITP as a manifestation</td>
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<tr>
<td>Cyclic thrombocytopenia</td>
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<tr>
<td>Autoimmune lymphoproliferative syndrome and its variants</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Evans syndrome</td>
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<tr>
<td>Antiphospholipid antibody syndrome</td>
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<tr>
<td>Neoplasia-associated immune thrombocytopenia</td>
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<tr>
<td>Thrombocytopenia associated with HIV</td>
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<tr>
<td>Neonatal immune thrombocytopenia</td>
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<tr>
<td>Alloimmune</td>
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<tr>
<td>Autoimmune (e.g., maternal ITP)</td>
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<tr>
<td>Drug-induced immune thrombocytopenia (including heparin-induced thrombocytopenia)</td>
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<tr>
<td>Posttransfusion purpura</td>
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<tr>
<td>Allergy and anaphylaxis</td>
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<tr>
<td>Posttransplant thrombocytopenia</td>
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<tr>
<td>Nonimmune thrombocytopenias</td>
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<tr>
<td>Thrombocytopenia of infection</td>
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<tr>
<td>Bacteremia or fungemia</td>
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<td>Viral infection</td>
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<td>Protozoan</td>
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<tr>
<td>Thrombotic microangiopathic disorders</td>
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<tr>
<td>Hemolytic-uremic syndrome</td>
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<tr>
<td>Eclampsia, HELLP syndrome</td>
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<tr>
<td>Thrombotic thrombocytopenic purpura</td>
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<tr>
<td>Bone marrow transplantation-associated microangiopathy</td>
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<tr>
<td>Drug-induced</td>
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<thead>
<tr>
<th>Combined Platelet and Fibrinogen Consumption Syndromes</th>
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<tbody>
<tr>
<td>Disseminated intravascular coagulation</td>
<td></td>
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<tr>
<td>Kasabach-Merritt syndrome</td>
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<tr>
<td>Virus-associated hemophagocytic syndrome</td>
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<table>
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<tr>
<th>Impaired Platelet Production</th>
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<tbody>
<tr>
<td>Hereditary disorders</td>
<td></td>
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<tr>
<td>Acquired disorders</td>
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<tr>
<td>Aplastic anemia</td>
<td></td>
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<tr>
<td>Myelodysplastic syndrome</td>
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<tr>
<td>Marrow infiltrative process—neoplasia</td>
<td></td>
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<tr>
<td>Osteoporosis</td>
<td></td>
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<tr>
<td>Nutritional deficiency states (iron, folate, vitamin B12, anorexia nervosa)</td>
<td></td>
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<tr>
<td>Drug- or radiation-induced thrombocytopenia</td>
<td></td>
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<tr>
<td>Neonatal hypoxia or placental insufficiency</td>
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<tr>
<th>Sequestration</th>
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<tbody>
<tr>
<td>Hypersplenism</td>
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<td>Hypothermia</td>
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<tr>
<td>Burns</td>
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</tbody>
</table>

HELLP, hemolysis, elevated liver enzymes, and low platelets; HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; VWD, von Willebrand disease.


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Table 484-2  Classification of Fetal and Neonatal Thrombocytopenias*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
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<tbody>
<tr>
<td>Fetal</td>
<td>Late-onset neonatal (&gt;72 hr)</td>
</tr>
<tr>
<td>Alloimmune thrombocytopenia</td>
<td>Late-onset sepsis</td>
</tr>
<tr>
<td>Congenital infection (e.g., CMV, toxoplasma, rubella, HIV)</td>
<td>NEC</td>
</tr>
<tr>
<td>Aneuploidy (e.g., trisomy 18, 13, or 21, or triploidy)</td>
<td>Congenital infection (e.g., CMV, toxoplasma, rubella, HIV)</td>
</tr>
<tr>
<td>Autoimmune condition (e.g., ITP, SLE)</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>Severe Rh hemolytic disease</td>
<td>Kasabach-Merritt syndrome</td>
</tr>
<tr>
<td>Congenital/inherited (e.g., Wiskott-Aldrich syndrome)</td>
<td>Metabolic disease (e.g., proprionic and methylmalonic acidemia)</td>
</tr>
<tr>
<td>Placental insufficiency (e.g., PET, IUGR, diabetes)</td>
<td>Congenital/inherited (e.g., TAR, CAMT)</td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
<td>Late-onset neonatal (&gt;72 hr)</td>
</tr>
<tr>
<td>Perinatal infection (e.g., Escherichia coli, GBS, herpes simplex)</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>DIC</td>
<td>Kasabach-Merritt syndrome</td>
</tr>
<tr>
<td>alloimmune thrombocytopenia</td>
<td>Metabolic disease (e.g., proprionic and methylmalonic acidemia)</td>
</tr>
<tr>
<td>Autoimmune condition (e.g., ITP, SLE)</td>
<td>Congenital/inherited (e.g., TAR, CAMT)</td>
</tr>
<tr>
<td>Congenital infection (e.g., CMV, toxoplasma, rubella, HIV)</td>
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</tr>
</tbody>
</table>

*The most common conditions are shown in bold.

CAMT, congenital amegakaryocytic thrombocytopenia; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; GBS, group B streptococcus; ITP, idiopathic thrombocytopenic purpura; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; PET, preeclampsia; SLE, systemic lupus erythematosus; TAR, thrombocytopenia with absent radii.

The most common cause of acute onset of thrombocytopenia in an otherwise well child is autoimmune idiopathic thrombocytopenic purpura (ITP).

**Epidemiology**

In a small number of children, estimated at 1 in 20,000, 1-4 wk after exposure to a common viral infection, an autoantibody directed against the platelet surface develops with resultant sudden onset of thrombocytopenia. A recent history of viral illness is described in 50-65% of cases of childhood ITP. The peak age is 1-4 yr, although the age ranges from early in infancy to the elderly. In childhood, males and females are equally affected. ITP seems to occur more often in late winter and spring after the peak season of viral respiratory illness.

**Pathogenesis**

Why some children develop the acute presentation of an autoimmune disease is unknown. The exact antigenic target for most such antibodies in most cases of childhood acute ITP remains undetermined. Although in chronic ITP, many patients demonstrate antibodies against the platelet glycoprotein complexes, GPIb-β, and GPIb-α. After binding of the antibody to the platelet surface, circulating antibody-coated platelets are recognized by the Fc receptor on splenic macrophages, ingested, and destroyed. Most common viruses have been described in association with ITP, including Epstein-Barr virus (see Chapter 254) and HIV (see Chapter 276). Epstein-Barr virus-related ITP is usually of short duration and follows the course of infectious mononucleosis. HIV-associated ITP is usually chronic. In some patients ITP appears to arise in children infected with *Helicobacter pylori* or rarely following vaccines.

**Clinical Manifestations**

The classic presentation of ITP is a previously healthy 1-4 yr old child who has sudden onset of generalized petechiae and purpura. The parents often state that the child was fine yesterday and now is covered with bruises and purple dots. There may be bleeding from the gums and mucous membranes, particularly with profound thrombocytopenia (platelet count <10 × 10^9/L). There is a history of a preceding viral infection 1-4 wk before the onset of thrombocytopenia. Findings on physical examination are normal unless ITP is complicated by severe thrombocytopenia, where there may be spontaneous bleeding or the possibility of a systemic illness, such as systemic lupus erythematosus (SLE), is more likely.

When the onset is insidious, especially in an adolescent, chronic ITP may develop. The presence of abnormal findings such as hepatosplenomegaly, bone or joint pain, remarkable lymphadenopathy, or palmar erythema suggests other diagnoses (leukemia, syndromes). When the onset is insidious, especially in an adolescent, chronic ITP is more likely.

**Outcome**

Severe bleeding is rare (<3% of cases in 1 large international study). In 70-80% of children who present with acute ITP, spontaneous resolution occurs within 6 mo. Therapy does not appear to affect the natural history of the illness. Fewer than 1% of patients develop an intracranial hemorrhage. Those who favor interventional therapy argue that the objective of early therapy is to raise the platelet count to >20 × 10^9/L and prevent the rare development of intracranial hemorrhage. There is no evidence that therapy prevents serious bleeding. Approximately 20% of children who present with acute ITP go on to have chronic ITP. The outcome/prognosis may be related more to age, as ITP in younger children is more likely to resolve whereas the development of chronic ITP in adolescents approaches 50%.

**Laboratory Findings**

Severe thrombocytopenia (platelet count <20 × 10^9/L) is common, and platelet size is normal or increased, reflective of increased platelet turnover (Fig. 484-3). In acute ITP, the hemoglobin value, white blood cell (WBC) count, and differential count should be normal. Hemoglobin may be decreased if there have been profuse nosebleeds or menorrhagia. Bone marrow examination shows normal granulocytic and erythrocytic series, with characteristically normal or increased...
numbers of megakaryocytes. Some of the megakaryocytes may appear to be immature and are reflective of increased platelet turnover. **Indications for bone marrow aspiration/biopsy** include an abnormal WBC count or differential or unexplained anemia as well as findings on history and physical examination suggestive of a bone marrow failure syndrome or malignancy. Other laboratory tests should be performed as indicated by the history and physical examination. HIV studies should be done in at-risk populations, especially sexually active teens. Platelet antibody testing is seldom useful in acute ITP. A direct antiglobulin test (Coombs) should be done if there is unexplained anemia to rule out Evans syndrome (autoimmune hemolytic anemia and thrombocytopenia) (see Chapter 458) or before instituting therapy with IV anti-D.

**DIAGNOSIS/DIFFERENTIAL DIAGNOSIS**

The well-appearing child with moderate to severe thrombocytopenia, an otherwise normal complete blood cell count (CBC), and normal findings on physical examination has a limited differential diagnosis that includes exposure to medication that induces drug-dependent antibodies, splenic sequestration because of previously unappreciated portal hypertension, and, rarely, early aplastic processes, such as Fanconi anemia (see Chapter 468). Other than congenital thrombocytopenia syndromes (see Chapter 484.8), such as thrombocytopenia-absent radius (TAR) syndrome and MYH9-related thrombocytopenia, most marrow processes that interfere with platelet production eventually cause abnormal synthesis of red blood cells (RBCs) and WBCs, and therefore manifest diverse abnormalities on the CBC. Disorders that cause increased platelet destruction on a nonimmune basis are usually serious systemic illnesses with obvious clinical findings (e.g., hemolytic-uremic syndrome [HUS], disseminated intravascular coagulation [DIC]) (see Table 483-1 in Chapter 483, and Fig. 484-2). Patients on heparin may develop heparin-induced thrombocytopenia. Isolated enlargement of the spleen suggests the potential for hypersplenism owing to either liver disease or portal vein thrombosis. Autoimmune thrombocytopenia may be an initial manifestation of SLE, HIV infection, common variable immunodeficiency, and, rarely, lymphoma or autoimmune lymphoproliferative syndrome. Wiskott-Aldrich syndrome (WAS; Chapter 126.2) must be considered in young males found to have thrombocytopenia with small platelets, particularly if there is a history of eczema and recurrent infection.

**TREATMENT**

There are no data showing that treatment affects either short- or long-term clinical outcome of ITP. Many patients with new-onset ITP have mild symptoms, with findings limited to petechiae and purpura on the skin, despite severe thrombocytopenia. Compared with untreated control subjects, treatment appears to be capable of inducing a more rapid rise in platelet count to the theoretically safe level of >20 × 10^9/L, although there are no data indicating that early therapy prevents intracranial hemorrhage. Antiplatelet antibodies bind to transfused platelets as well as they do to autologous platelets. Thus, platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present. Initial approaches to the management of ITP include the following:

1. No therapy other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier. This approach emphasizes the usually benign nature of ITP and avoids the therapeutic roller coaster that ensues once interventional therapy is begun. This approach is far less costly, and side effects are minimal.

2. Per the American Society of Hematology Guidelines: “A single dose of IVIG [intravenous immunoglobulin] (0.8-1.0 g/kg) or a short course of corticosteroids should be used as first-line treatment.” IVIG at a dose of 0.8-1.0 g/kg/day for 1-2 days induces a rapid rise in platelet count (usually >20 × 10^9/L) in 95% of patients within 48 hr. IVIG appears to induce a response by downregulating Fc-mediated phagocytosis of antibody-coated platelets. IVIG therapy is both expensive and time-consuming to administer. Additionally, after infusion, there is a high frequency of headaches and vomiting, suggestive of IVIG-induced aseptic meningitis.

3. Prednisone. Corticosteroid therapy has been used for many years to treat acute and chronic ITP in adults and children. Doses of prednisone of 1-4 mg/kg/24 hr appear to induce a more rapid rise in platelet count than in untreated patients with ITP. Corticosteroid therapy is usually continued for short course until a rise in platelet count to >20 × 10^9/L has been achieved to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis.

4. Intravenous anti-D therapy. For Rh-positive patients, IV anti-D at a dose of 50-75 μg/kg causes a rise in platelet count to >20 × 10^9/L in 80-90% of patients within 48-72 hr. When given to Rh-positive individuals, IV anti-D induces mild hemolytic anemia. RBC-antibody complexes bind to macrophage Fc receptors and interfere with platelet destruction, thereby causing a rise in platelet count. IV anti-D is ineffective in Rh-negative patients. Rare life-threatening episodes of intravascular hemolysis have occurred in children and adults following infusion of IV anti-D. Each of these medications may be used to treat ITP exacerbations, which commonly occur several weeks after an initial course of therapy. In the special case of intracranial hemorrhage, multiple modalities should be used, including platelet transfusion, IVIG, high-dose corticosteroids, and prompt consultation by neurosurgery and surgery.
remains rare, and there are no data showing that treatment actually reduces its incidence.

The role of splenectomy in ITP should be reserved for 1 of 2 circumstances. The older child (≥4 yr) with severe ITP that has lasted >1 yr (chronic ITP) and whose symptoms are not easily controlled with therapy is a candidate for splenectomy. Splenectomy must also be considered when life-threatening hemorrhage (intracranial hemorrhage) complicates acute ITP, if the platelet count cannot be corrected rapidly with transfusion of platelets and administration of IVIG and corticosteroids. Splenectomy is associated with a lifelong risk of overwhelming postsplenectomy infection caused by encapsulated organisms, increased risk of thrombosis, and the potential development of pulmonary hypertension in adulthood. As an alternative to splenectomy, rituximab has been used off-label in children to treat chronic ITP. In 30-40% of children, rituximab has induced a partial or complete remission.

**CHRONIC AUTOIMMUNE THROMBOCYTOPENIC PURPURA**

Approximately 20% of patients who present with acute ITP have persistent thrombocytopenia for >12 mo and are said to have chronic ITP. At that time, a careful reevaluation for associated disorders should be performed, especially for autoimmune disease, such as SLE; chronic infectious disorders, such as HIV; and nonimmune causes of chronic thrombocytopenia, such as type 2B and platelet-type von Willebrand disease, X-linked thrombocytopenia, autoimmune lymphoproliferative syndrome, common variable immunodeficiency syndrome, autosomal macrothrombocytopenia, and WAS (also X-linked). The presence of coexisting H. pylori infection should be considered and, if found, treated. Therapy should be aimed at controlling symptoms and preventing serious bleeding. In ITP, the spleen is the primary site of both antiplatelet antibody synthesis and platelet destruction. Splenectomy is successful in inducing complete remission in 64-88% of children with chronic ITP. This effect must be balanced against the lifelong risk of overwhelming postsplenectomy infection. This decision is often affected by quality of life issues, as well as the ease with which the child can be managed using medical therapy, such as IVIG, corticosteroids, IV anti-D, or rituximab. Two effective agents that act to stimulate thrombopoiesis, romiplostin and eltrombopag (see Fig. 484-1), are approved by the FDA to treat adults with chronic ITP. Preliminary data using thrombopoietic agents in children are encouraging.

**Bibliography is available at Expert Consult.**

### 484.2 Drug-Induced Thrombocytopenia

**J. Paul Scott**

A number of drugs are associated with immune thrombocytopenia as the result of either an immune process or megakaryocyte injury. Some common drugs used in pediatrics that cause thrombocytopenia include valproic acid, phenytoin, carbamazepine, sulfonamides, vancomycin, and trimethoprim-sulfamethoxazole. Heparin-induced thrombocytopenia (and, rarely, an associated thrombosis) is seldom seen in pediatrics, but it occurs when, after exposure to heparin, the patient has an antibody directed against the heparin–platelet factor 4 complex. Recommended treatment for heparin-induced thrombocytopenia in adults includes argatroban, lepirudin, or danaparoid.

**Bibliography is available at Expert Consult.**

### 484.3 Nonimmune Platelet Destruction

**J. Paul Scott**

The syndromes of DIC (see Chapter 483), HUS (see Chapters 484.4 and 518), and thrombotic thrombocytopenic purpura (TTP) (see Chapter 484.5) share the hematologic picture of a thrombotic microangiopathy in which there is RBC destruction and consumptive thrombocytopenia caused by platelet and fibrin deposition in the microvasculature. The microangiopathic hemolytic anemia is characterized by the presence of RBC fragments, including helmet cells, schistocytes, spherocytes, and burr cells.

#### 484.4 Hemolytic-Uremic Syndrome

See Chapter 518.

#### 484.5 Thrombotic Thrombocytopenic Purpura

**J. Paul Scott**

TTP is a rare pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, abnormal renal function, and central nervous system changes that is clinically similar to HUS, although TTP can be congenital, it usually presents in adults and occasionally in adolescents. Microvascular thrombi within the central nervous system cause subtle, shifting neurologic signs that vary from changes in affect and orientation to aphasia, blindness, and seizures. Initial manifestations are often nonspecific (weakness, pain, emesis); prompt recognition of this disorder is critical. Laboratory findings provide important clues to the diagnosis and show microangiopathic hemolytic anemia characterized by morphologically abnormal RBCs, with schistocytes, spherocytes, helmet cells, and an elevated reticulocyte count in association with thrombocytopenia. Coagulation studies are usually nondiagnostic. Blood urea nitrogen and creatinine are sometimes elevated. The treatment of TTP is plasmapheresis (plasma exchange), which is effective in 80-95% of cases. Treatment with plasmapheresis should be instituted on the basis of thrombocytopenia and microangiopathic hemolytic anemia even if other symptoms are not yet present. Rituximab, corticosteroids, and splenectomy are reserved for refractory cases.

The majority of cases of TTP are caused by an autoantibody-mediated deficiency of a metalloproteinase (ADAMTS-13) that is responsible for cleaving the high-molecular-weight multimers of VWF and appears to play a pivotal role in the evolution of the thrombotic microangiopathy. In contrast, levels of the metalloproteinase in HUS are usually normal. Congenital deficiency of the metalloproteinase causes rare familial cases of TTP/HUS, usually manifested as recurrent episodes of thrombocytopenia, hemolytic anemia, and renal involvement, with or without neurologic changes, that often present in infancy after an intercurrent illness. Abnormalities of the complement system have now also been implicated in rare cases of familial TTP. ADAMTS-13 deficiency can be treated by repeated infusions of fresh-frozen plasma.

**Bibliography is available at Expert Consult.**

### 484.6 Kasabach-Merritt Syndrome

**J. Paul Scott**

See also Chapter 650.

The association of a giant hemangioma with localized intravascular coagulation causing thrombocytopenia and hypofibrinogenemia is called Kasabach-Merritt syndrome. In most patients, the site of the hemangioma is obvious, but retroperitoneal and intraabdominal hemangiomas may require body imaging for detection. Inside the hemangioma there is platelet trapping and activation of coagulation, with fibrinogen consumption and generation of fibrin(ogen) degradation products. Arteriovenous malformation within the lesions can cause heart failure. Pathologically, Kasabach-Merritt syndrome appears to develop more often as a result of a kaposiform hemangioendothelioma
**Bibliography**


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or tufted hemangioma rather than a simple hemangioma. The peripheral blood smear shows microangiopathic changes. Multiple modalities have been used to treat Kasabach-Merritt syndrome, including propranolol, surgical excision (if possible), laser photocoagulation, high-dose corticosteroids, local radiation therapy, antiangiogenic agents, such as interferon-α, and vincristine. Over time, most patients who present in infancy have regression of the hemangioma. Treatment of the associated coagulopathy may benefit from a trial of antifibrinolytic therapy with e-aminocaproic acid (Amicar).

484.7 Sequestration
J. Paul Scott

Thrombocytopenia develops in individuals with massive splenomegaly because the spleen acts as a sponge for platelets and sequesters large numbers. Most such patients also have mild leukopenia and anemia on CBC. Individuals who have thrombocytopenia caused by splenic sequestration should undergo a work-up to diagnose the etiology of splenomegaly, including infectious, inflammatory, infiltrative, neoplastic, obstructive, and hemolytic causes.

484.8 Congenital Thrombocytopenic Syndromes
J. Paul Scott

See Table 484-2.

Congenital amegakaryocytic thrombocytopenia (CAMT) usually manifests within the 1st few days to week of life, when the child presents with petechiae and purpura caused by profound thrombocytopenia. CAMT is caused by a rare defect in hematopoiesis as a result of a mutation in the stem cell TPO receptor (MPL). Other than skin and mucous membrane abnormalities, findings on physical examination are normal. Examination of the bone marrow shows an absence of megakaryocytes. These patients often progress to marrow failure (aplasia) over time. Hematopoietic stem cell transplantation is curative.

TAR syndrome consists of thrombocytopenia (absence or hypoplasia of megakaryocytes) that presents in early infancy with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening (Fig. 484-4). Many such individuals also have other skeletal abnormalities of the ulna, radius, and lower extremities. Thumbs are present. Intolerance to cow’s milk formula (present in 50%) may complicate management by triggering gastrointestinal bleeding, increased thrombocytopenia, eosinophilia, and a leukemoid reaction. The thrombocytopenia of TAR syndrome frequently remits over the 1st few yrs of life. The molecular basis of TAR syndrome remains to be defined. A few patients have been reported to have a syndrome of amegakaryocytic thrombocytopenia with radioulnar synostosis caused by a mutation in the HOXA11 gene. Different from TAR syndrome, this mutation causes marrow aplasia.

WAS is characterized by thrombocytopenia, with tiny platelets, eczema, and recurrent infection as a consequence of immune deficiency (see Chapter 126.2). WAS is inherited as an X-linked disorder, and the gene for WAS has been sequenced. The WAS protein appears to play an integral role in regulating the cytoskeletal architecture of both platelets and T lymphocytes in response to receptor-mediated cell signaling. The WAS protein is common to all cells of hematopoietic lineage. Molecular analysis of families with X-linked thrombocytopenia has shown that many affected members have a point mutation within the WAS gene, whereas individuals with the full manifestation of WAS have large gene deletions. Examination of the bone marrow in WAS shows the normal number of megakaryocytes, although they may have bizarre morphologic features. Transfused platelets have a normal life span. Splenectomy often corrects the thrombocytopenia, suggesting that the platelets formed in WAS have accelerated destruction. After splenectomy, these patients are at increased risk for overwhelming infection and require lifelong antibiotic prophylaxis against encapsulated organisms. Approximately 5-15% of patients with WAS develop lymphoreticular malignancies. Successful hematopoietic stem cell transplantation cures WAS. X-linked macrothrombocytopenia and dyserythropoiesis have been linked to mutations in the GATA-1 gene, an erythroid and megakaryocytic transcription factor.

MYH9-related thrombocytopenia: A diverse number of hereditary thrombocytopenia syndromes, given names such as Sebastian, Epstein,
May–Hegglin, and Fechtner syndromes, are characterized by autosomal dominant macrothrombocytopenia, neutrophil inclusion bodies, and a variety of physical anomalies, including sensorineural deafness, renal disease, and/or eye disease. These have all been shown to be caused by different mutations in the MYH9 gene (nonmuscle myosin-IIa heavy chain). The thrombocytopenia is usually mild and not progressive. Some other individuals with recessively inherited macrothrombocytopenia have abnormalities in chromosome 22q11. Mutations in the gene for glycoprotein Ib, an essential component of the platelet VWF receptor, can result in Bernard–Soulier syndrome (see Chapter 484.13).

Bibliography is available at Expert Consult.

484.9 Neonatal Thrombocytopenia

J. Paul Scott

See also Chapter 103.4.

Thrombocytopenia in the newborn rarely is indicative of a primary disorder of megakaryopoiesis but more often is the result of either systemic illness or transfer of maternal antibodies directed against fetal platelets (see Table 484-2). Neonatal thrombocytopenia often occurs in association with congenital viral infection, especially rubella; cytomegalovirus; protozoal infection, such as toxoplasmosis; syphilis; and perinatal bacterial infection, especially those caused by Gram-negative bacilli. Thrombocytopenia associated with DIC may be responsible for severe spontaneous bleeding. The constellation of marked thrombocytopenia and abnormal abdominal findings is common in necrotizing enterocolitis and other causes of necrotic bowel. Thrombocytopenia in an ill child requires a prompt search for viral and bacterial pathogens.

Antibody-mediated thrombocytopenia in the newborn occurs because of transplacental transfer of maternal antibodies directed against fetal platelets. Neonatal alloimmune thrombocytopenic purpura (NATP) is caused by the development of maternal antibodies against antigens present on fetal platelets that are shared with the father and recognized as foreign by the maternal immune system. This is the platelet equivalent of Rh disease of the newborn. The incidence of NATP is 1/4,000–5,000 live births. The clinical manifestations of NATP are those of an apparently well child who, within the 1st few days after delivery, has generalized petechiae and purpura. Laboratory studies show a normal maternal platelet count, yet moderate to severe thrombocytopenia before delivery appears to predict a higher risk of fetal thrombocytopenia. In mothers who have had splenectomy for ITP, the maternal platelet count may be normal and is not predictive of fetal thrombocytopenia.

Treatment includes prenatal administration of corticosteroids to the mother and administration of IVIG and sometimes corticosteroids to the infant after delivery. Thrombocytopenia in an infant, whether a result of NATP or maternal ITP, usually resolves within 2–4 mo after delivery. The period of highest risk is the immediate perinatal period.

Two syndromes of congenital failure of platelet production often present in the newborn period. In CAMT, the newborn manifests petechiae and purpura shortly after birth. Findings on physical examination are otherwise normal. Megakaryocytes are absent from the bone marrow. This syndrome is caused by a mutation in the megakaryocyte TPO receptor that is essential for development of all hematopoietic cell lines. Pancytopenia eventually develops, and hematopoietic stem cell transplantation is curative. TAR syndrome consists of thrombocytopenia that presents in early infancy, with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening. Thumbs are present. In many such individuals, there are also other skeletal abnormalities of the lower extremities. Intolerance to cow’s milk formula is present in 50% of patients. TAR syndrome frequently remits over the 1st few yr of life (see Chapter 484.8) (see Fig. 484-4).

Bibliography is available at Expert Consult.

484.10 Thrombocytopenia from Acquired Disorders Causing Decreased Production

J. Paul Scott and Veronica Flood

Disorders of the bone marrow that inhibit megakaryopoiesis usually affect RBC and WBC production. Infiltrative disorders, including malignancies, such as acute lymphocytic leukemia, histiocytosis, lymphomas, and storage disease, usually cause either abnormalities on physical examination (lymphadenopathy, hepatosplenomegaly, or masses) or abnormalities of the WBC count, or anemia. Aplastic processes may present as isolated thrombocytopenia, although there are usually clues on the CBC (leukopenia, neutropenia, anemia, or macrocytosis). Children with constitutional aplastic anemia (Fanconi anemia) often have abnormalities on examination, including radial anomalies, other skeletal anomalies, short stature, microcephaly, and hyperpigmentation. Bone marrow examination should be performed when thrombocytopenia is associated with abnormalities found on physical examination or on examination of the other blood cell lines.

484.11 Platelet Function Disorders

J. Paul Scott

Bleeding time and the platelet function analyzer (PFA-100) are the only commonly available tests to screen for abnormal platelet function. Bleeding time measures the interaction of platelets with the blood vessel wall and thus is affected by both platelet count and platelet function. The predictive value of bleeding time is problematic because bleeding time is dependent on a number of other factors, including the skill of the technician and the cooperation of the patient, often a challenge in the infant or young child. A normal bleeding time does not rule out a mild platelet function defect in a clinically symptomatic individual. The PFA-100 measures platelet adhesion and aggregation in whole blood at high shear when the blood is exposed to either
Bibliography
Bibliography


Chapter 484  •  Platelet and Blood Vessel Disorders

484.12 Acquired Disorders of Platelet Function

J. Paul Scott

A number of systemic illnesses are associated with platelet dysfunction, most commonly, liver disease, kidney disease (uremia), and disorders that trigger increased amounts of fibrin degradation products. These disorders frequently cause prolonged bleeding time and are often associated with other abnormalities of the coagulation mechanism. The most important element of management is to treat the primary illness. If treatment of the primary process is not feasible, infusions of desmopressin have been helpful in augmenting hemostasis and correcting bleeding time. In some patients, transfusions of platelets and/or cryoprecipitate have also been helpful in improving hemostasis.

Many drugs alter platelet function. The most commonly used drug in adults that alters platelet function is acetylsalicylic acid (aspirin). Aspirin irreversibly acetylates the enzyme cyclo-oxygenase, which is critical in the formation of thromboxane A₂. Aspirin usually causes moderate platelet dysfunction that becomes more prominent if there is another abnormality of the hemostatic mechanism. In children, commonly used drugs that affect platelet function include other nonsteroidal antiinflammatory drugs, valproic acid, and high-dose penicillin. Specific agents to inhibit platelet function therapeutically include those that block the platelet ADP receptor (clopidogrel) and β₃-receptor antagonists, as well as aspirin.

484.13 Congenital Abnormalities of Platelet Function

J. Paul Scott

Severe platelet function defects usually present with petechiae and purpura shortly after birth, especially after vaginal delivery. Defects in the platelet GPIb complex (the VWF receptor) or the αIIb-β₃ complex (the fibrinogen receptor) cause severe congenital platelet dysfunction.

Bernard-Soulier syndrome, a severe congenital platelet function disorder, is caused by absence or severe deficiency of the VWF receptor (GPIb complex) on the platelet membrane. This syndrome is characterized by thrombocytopenia, with giant platelets and markedly prolonged bleeding time (>20 min) or PFA-100 closure time. Platelet aggregation tests show absent ristocetin-induced platelet aggregation, but normal aggregation to all other agonists. Ristocetin induces the binding of VWF to platelets and agglutinates platelets. Results of studies of VWF are normal. The GPIb complex interacts with the platelet cytoskeleton; a defect in this interaction is believed to be the cause of the large platelet size. Bernard-Soulier syndrome is inherited as an autosomal recessive disorder. Genetic mutations causing Bernard-Soulier syndrome are usually identified in the genes forming the GPIb complex of glycoproteins Ibo, Ibβ, V, and IX.

Glanzmann thrombasthenia is a congenital disorder associated with severe platelet dysfunction that yields prolonged bleeding time and a normal platelet count. Platelets have normal size and morphologic features on the peripheral blood smear, and closure times for PFA-100 or bleeding time are markedly abnormal. Aggregation studies show abnormal or absent aggregation with all agonists used except ristocetin, because ristocetin agglutinates platelets and does not require a metabolically active platelet. This disorder is caused by deficiency of the platelet fibrinogen receptor αIIb-β₃, the major integrin complex on the platelet surface that undergoes conformational changes by inside out signaling when platelets are activated. Fibrinogen binds to this complex when the platelet is activated and causes platelets to aggregate. Caused by identifiable mutations in the genes for αIIb or β₃, this disorder is inherited in an autosomal recessive manner. For both Bernard-Soulier syndrome and Glanzmann thrombasthenia, the diagnosis is confirmed by flow cytometric analysis of the patient’s platelet glycoproteins.

Hereditary deficiency of platelet storage granules occurs in 2 well-characterized but rare syndromes that involve deficiency of intracytoplasmic granules. Dense body deficiency is characterized by absence of the granules that contain ADP, ATP, Ca²⁺, and serotonin. This disorder is diagnosed by the finding that ATP is not released on platelet aggregation studies and ideally is characterized by electron microscopic studies. Gray platelet syndrome is caused by the absence of platelet α granules, resulting in large platelets that are large and appear gray on Wright stain of peripheral blood. In this rare syndrome, aggregation and release are absent with most agonists other than thrombin and ristocetin. Electron microscopic studies are diagnostic.

OTHER HEREDITARY DISORDERS OF PLATELET FUNCTION

Abnormalities in the pathways of platelet signaling/activation and release of granular contents cause a heterogeneous group of platelet function defects that are usually manifested as increased bruising, epistaxis, and/or menorrhagia. Symptoms may be subtle and are often made more obvious by high-risk surgery, such as tonsillectomy or adenoidectomy, or by administration of nonsteroidal antiinflammatory drugs. In the laboratory, bleeding time is variable and closure time as measured by the PFA-100 is frequently, but not always, prolonged. Platelet aggregation studies show deficient aggregation with 1 or 2 agonists and/or abnormal release of granular contents.

The formation of thromboxane from arachidonic acid after the activation of phospholipase is critical to normal platelet function. Deficiency or dysfunction of enzymes, such as cyclo-oxygenase and thromboxane synthase, which metabolize arachidonic acid, causes abnormal platelet function. In the aggregometer, platelets from such patients do not aggregate in response to arachidonic acid.

The most common platelet function defects are those characterized by variable bleeding time/PFA closure times and abnormal aggregation with 1 or 2 agonists, usually ADP and/or collagen. These patients have normal aggregation with thrombin receptor peptide. Some of these individuals have only decreased release of ATP from intracytoplasmic granules; the significance of this finding is debated.

TREATMENT OF PATIENTS WITH PLATELET DYSFUNCTION

Successful treatment depends on the severity of both the diagnosis and the hemorrhagic event. In all but severe platelet function defects, desmopressin 0.3 μg/kg IV may be used for mild to moderate bleeding...
In addition to its effect on stimulating levels of VWF and factor VIII, desmopressin corrects bleeding time and augments hemostasis in many individuals with mild to moderate platelet function defects. For individuals with Bernard-Soulier syndrome or Glanzmann thrombasthenia, platelet transfusions of 1 unit/5-10 kg corrects the defect in hemostasis and may be lifesaving. Rarely, antibodies develop to the deficient platelet protein, rendering the patient refractory to the transfused platelets. In such patients, the off-label use of recombinant factor VIIa has been effective, and this treatment is undergoing clinical trials. In both conditions, hematopoietic stem cell transplantation has been curative.

Bibliography is available at Expert Consult.

484.14 Disorders of the Blood Vessels

J. Paul Scott

Disorders of the vessel walls or supporting structures mimic the findings of a bleeding disorder although coagulation studies are usually normal. The findings of petechiae and purpuric lesions in such patients are often attributable to an underlying vasculitis/vasculopathy. Skin biopsy can be particularly helpful in elucidating the type of vascular pathology.

HENOECH-SCHÖNLEIN PURPURA
See Chapter 167.1.

EHLERS-DANLOS SYNDROME
See Chapter 659.

OTHER ACQUIRED DISORDERS
Scurvy, chronic corticosteroid therapy, and severe malnutrition are associated with “weakening” of the collagen matrix that supports the blood vessels. Therefore, these factors are associated with easy bruising, and particularly in the case of scurvy, bleeding gums and loosening of the teeth. Lesions of the skin that initially appear to be petechiae and purpura may be seen in vasculitic syndromes, such as SLE.

Bibliography is available at Expert Consult.
Bibliography
Bibliography
Chapter 485
Anatomy and Function of the Spleen
Amanda M. Brandow and Bruce M. Camitta

ANATOMY
The splenic precursor is recognizable by 5 wk of gestation. At birth, the spleen weighs approximately 11 g. Thereafter, it enlarges until puberty, reaching an average weight of 135 g, and then diminishes in size during adulthood. Approximately 15% of patients will have an accessory spleen. The major splenic components are a lymphoid compartment (white pulp) and a filtering system (red pulp). The white pulp consists of periarterial lymphatic sheaths of T lymphocytes with embedded germinal centers containing B lymphocytes. The red pulp has a skeleton of fixed reticular cells, mobile macrophages, partially collapsed endothelial passages (cords of Billroth), and splenic sinuses. A marginal zone rich in dendritic (antigen-presenting) cells separates the red pulp from the white pulp. The splenic capsule contains smooth muscle and contracts in response to epinephrine. Approximately 10% of the blood delivered to the spleen flows rapidly through a closed vascular network. The other 90% flows more slowly through an open system (the splenic cords), where it is filtered through 1-5 µm slits before entering the splenic sinuses.

FUNCTION
The unique anatomy and blood flow of the spleen enable it to perform reservoir, filtering, and immunologic functions. The spleen receives 5-6% of the cardiac output, but normally contains only 25 mL of blood. It can retain much more when it enlarges leading to cytopenias. Hematopoiesis is a major splenic function at 3-6 mo of fetal life but then disappears. Splenic hematopoiesis can be resumed in patients with myelofibrosis or severe hemolytic anemia. Factor VIII and one-third of the circulating platelet mass are sequestered in the spleen and can be released by stress or epinephrine injection. Thrombocytosis and leukocytosis occur with loss of the splenic reservoir function. A high platelet count after the loss of splenic function or splenectomy is not associated with an increased risk of thrombosis in children.

Slow blood flow past macrophages and through small openings in the sinus walls facilitates the filtering functions of the spleen. Excess membrane is removed from young red blood cells (RBCs); loss of this function is characterized by target cells, poikilocytosis, and decreased osmotic fragility. The spleen is the primary site for destruction of old RBCs; this function is assumed by other reticuloendothelial cells after splenectomy. The spleen also removes damaged/abnormal red cells (such as spherocytes and antibody-coated RBCs) and damaged/senescent platelets. Intracytoplasmic inclusions may be removed from RBCs without cell lysis. Functional or anatomic hyposplenia is characterized by continued circulation of cells containing nuclear remnants (Howell-Jolly bodies), denatured hemoglobin (Heinz bodies), and other debris in RBCs. This debris may appear as “pits” on indirect microscopy.

The spleen plays a large role in host defense against infection. The spleen is the largest lymphoid organ in the body and contains nearly half of the body’s total immunoglobulin-producing B lymphocytes. The spleen processes foreign material to stimulate production of opsonizing antibody. Properdin and tuftsin are also produced in the spleen. Thus, young (nonimmune) or hyposplenic individuals are at increased risk for sepsis caused by pneumococci and other encapsulated bacteria. The spleen can also use phagocytosis to trap and destroy intracellular parasites. The spleen has a minor role in antibody response to intramuscularly or subcutaneously injected antigens but is required for early antibody production after exposure to intravenous antigens. The spleen may be an important site of antibody production in immune thrombocytopenia purpura.

Bibliography is available at Expert Consult.
Bibliography


A soft, thin spleen is palpable in 15% of neonates, 10% of normal children, and 5% of adolescents. In most individuals, the spleen must be 2-3 times its normal size before it is palpable. The spleen is best examined when standing on the right side of a supine patient by
palpating across the abdomen as the patient inspires deeply or with the patient in the right lateral decubitus position. A splenic edge felt more than 2 cm below the left costal margin is abnormal. An enlarged spleen might descend into the pelvis; when splenomegaly is suspected, the abdominal examination should begin at a lower starting point. Superficial abdominal venous distention may be present when splenomegaly is a result of portal hypertension. Patients may also complain of left upper quadrant pain as the spleen enlarges. Radiologic detection or confirmation of splenic enlargement is done with ultrasonography, CT, or technetium-99 sulfur colloid scan. The latter also assesses splenic function.

**DIFFERENTIAL DIAGNOSIS**

Table 486-1 lists specific causes of splenomegaly. A thorough history with a focus on systemic complaints (fever, night sweats, malaise, weight loss) and a complete physical exam (with special attention to adenopathy), in combination with a complete blood count and careful review of the peripheral smear can help guide diagnosis.

**Pseudosplenomegaly**

Abnormally long mesenteric connections may produce a wandering or potic spleen. An enlarged left lobe of the liver, a left upper quadrant mass, or a splenic hematoma may be mistaken for splenomegaly.

**Table 486-1** Differential Diagnosis of Splenomegaly by Pathophysiology

<table>
<thead>
<tr>
<th>ANATOMIC LESIONS</th>
<th>Parasitic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysts, pseudocysts</td>
<td>Malaria</td>
</tr>
<tr>
<td>Hamartomas</td>
<td>Toxoplasmosis, especially congenital</td>
</tr>
<tr>
<td>Polysplenia syndrome</td>
<td>Toxocara canis, Toxocara cati (visceral larva migrans)</td>
</tr>
<tr>
<td>Hemangiomas and lymphangiomas</td>
<td>Leishmaniasis (kala-azar)</td>
</tr>
<tr>
<td>Hematoma or rupture (traumatic)</td>
<td>Schistosomiasis (hepatic-portal involvement)</td>
</tr>
<tr>
<td>Peliosis</td>
<td>Trypanosomiasis</td>
</tr>
<tr>
<td>HYPERPLASIA CAUSED BY HEMATOLOGIC DISORDERS</td>
<td>Fascioliasis</td>
</tr>
<tr>
<td>Acute and Chronic Hemolysis*</td>
<td>Babesiosis</td>
</tr>
<tr>
<td>Hemoglobinopathies (sickle cell disease in infancy with or without sequestration crisis and sickle variants, thalassemia major, unstable hemoglobin)</td>
<td>IMMUNOLOGIC AND INFLAMMATORY PROCESSES*</td>
</tr>
<tr>
<td>Erythrocyte membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Erythrocyte enzyme deficiencies (severe G6PD deficiency, pyruvate kinase deficiency)</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Immune hemolysis (autoimmune and isoimmune hemolysis)</td>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Chronic Iron Deficiency</td>
<td>Serum sickness</td>
</tr>
<tr>
<td>Extramedullary Hematopoiesis</td>
<td>Drug hypersensitivity, especially to phenytoin</td>
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<tr>
<td>Myeloproliferative diseases: CML, juvenile CML, myelofibrosis with myeloid metaplasia, polycythemia vera</td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>Patients receiving granulocyte and granulocyte-macrophage colony-stimulating factors</td>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>INFECTIONS†</td>
<td>Amyloidosis</td>
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<tr>
<td>Bacterial</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Acute sepsis: Salmonella typhi, Streptococcus pneumoniae, Haemophilus influenzae type b, Staphylococcus aureus</td>
<td>Autoimmune lymphoproliferative syndrome</td>
</tr>
<tr>
<td>Chronic infections: infective endocarditis, chronic meningococcemia, brucellosis, tularemia, cat-scratch disease</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Local infections: splenic abscess (S. aureus, streptococci, less often Salmonella species, polymicrobial infection), pyogenic liver abscess (anaerobic bacteria, Gram-negative enteric bacteria), cholangitis</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Viral</td>
<td>Cryoglobulinemia</td>
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<td>Acute viral infections, especially in children</td>
<td>Sjögren syndrome</td>
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<td>Congenital CMV, herpes simplex, rubella</td>
<td>Graft-versus-host disease</td>
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<tr>
<td>Hepatitis A, B, and C; CMV</td>
<td>Drug hypersensitivity, especially to phenytoin</td>
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<td>EBV</td>
<td>Serum sickness</td>
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<td>Viral hemophagocytic syndromes: CMV, EBV, HHV-6</td>
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<td>HIV</td>
<td>Mixed connective tissue disease</td>
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<td>Spirochetal</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Syphilis, especially congenital syphilis</td>
<td>Systemic lupus erythematosus</td>
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<td>Leptospirosis</td>
<td>IMMUNOLOGIC</td>
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<td>Rickettsial</td>
<td>Babesiosis</td>
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<td>Rocky Mountain spotted fever</td>
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<td>Q fever</td>
<td>Trypanosomiasis</td>
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<td>Typhus</td>
<td>Schistosomiasis</td>
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<td>Fungal/Mycobacterial</td>
<td>Leishmaniasis (kala-azar)</td>
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<td>Miliary tuberculosis</td>
<td>Toxocara cati, Toxocara canis (visceral larva migrans)</td>
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<td>Disseminated histoplasmosis</td>
<td>Schistosomiasis (hepatic-portal involvement)</td>
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<tr>
<td>South American blastomycosis</td>
<td>Malaria</td>
</tr>
<tr>
<td>Systemic candidiasis (in immunosuppressed patients)</td>
<td>Parasitic</td>
</tr>
</tbody>
</table>

*Common.

†Chronic or recurrent infection suggests underlying immunodeficiency.

CML, chronic myelogenous leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus.
Splenic cysts may contribute to splenomegaly or mimic it; these may be congenital (epidermoid) or acquired (pseudocyst) after trauma or infarction. Cysts are usually asymptomatic and are found on radiologic evaluation. Splenosis after splenic rupture or an accessory spleen (present in 15% of normal individuals) may also mimic splenomegaly; most are not palpable. The syndrome of congenital polysplenism includes cardiac defects, left-sided organ anomalies, bilobed lungs, biliary atresia, and pseudosplenomegaly (see Chapter 431.11).

**Hypersplenism**

Increased splenic function (sequestration or destruction of circulating cells) can result in peripheral blood cytopenias (thrombocytopenia, neutropenia, anemia), increased bone marrow activity, and splenomegaly. It is usually secondary to another disease and may be cured by treatment of the underlying condition or, if absolutely necessary, moderated by splenectomy.

**Congestive Splenomegaly (Banti Syndrome)**

Splenomegaly may result from obstruction in the hepatic, portal, or splenic veins leading to hypersplenism. Wilson disease (see Chapter 357.2), galactosemia (see Chapter 87.2), biliary atresia (see Chapter 356.1), and α₁-antitrypsin deficiency (see Chapter 357) may result in hepatic inflammation, fibrosis, and vascular obstruction. Congenital abnormalities (absence or hypoplasia) of the portal or splenic veins may cause vascular obstruction. Septic omphalitis or thrombophlebitis (spontaneous or as a result of umbilical venous catheterization in neonates) may result in secondary obliteration of these vessels. Splenic venous flow may be obstructed by masses of sickled erythrocytes leading to infarction. When the spleen is the site of vascular obstruction, splenectomy cures hypersplenism. However, since obstruction usually is in the hepatic or portal systems, portacaval shunting may be more helpful, because both portal hypertension and thrombocytopenia contribute to variceal bleeding.

Bibliography is available at Expert Consult.
Bibliography

HYPOSPLENISM

Congenital absence of the spleen is associated with complex cyanotic heart defects, dextrocardia, bilateral trilobed lungs, and heterotopic abdominal organs (Ivemark syndrome; see Chapter 431.11). Splenic function is usually normal in children with congenital polysplenia. Functional hyposplenism may occur in normal neonates, especially premature infants. Children with sickle cell hemoglobinopathies (see Chapter 462.1) may have splenic hypofunction as early as 6 mo of age. Initially, this is caused by vascular obstruction, which can be reversed with red blood cell (RBC) transfusion or hydroxyurea. The spleen eventually autoinfarcts and becomes fibrotic and permanently nonfunctional. Functional hyposplenism may also occur in malaria (see Chapter 288), after irradiation to the left upper quadrant, and when the reticuloendothelial function of the spleen is overwhelmed (as in severe hemolytic anemia or metabolic storage disease). Splenic hypofunction has been reported occasionally in patients with autoimmune diseases (i.e., rheumatoid arthritis, lupus, sarcoidosis), nephritis, inflammatory bowel disease, celiac disease, chronic hepatitis, Pearson syndrome, Fanconi anemia, and graft-versus-host disease) (Table 487-1).

Splenectomy

Injury to the spleen may occur with abdominal trauma. Small splenic capsular tears may cause abdominal or referred left shoulder pain as a result of diaphragmatic irritation by blood. Larger tears result in more severe blood loss, with similar pain and signs of hypovolemic shock. Previously enlarged spleens (as in patients with infectious mononucleosis) are more likely to rupture with minor trauma. Patients with splenomegaly should avoid contact sports and other activities that increase the risk of splenic trauma. CT scan with IV contrast is the best imaging modality to assess splenic trauma.

Treatment of a small capsular injury should include careful observation with attention to changes in vital signs or abdominal findings, serial hemoglobin determinations, and the availability of prompt surgical intervention if a patient’s condition deteriorates (see Chapter 72).

Table 487-1

<table>
<thead>
<tr>
<th>Diseases Associated with Hyposplenism or Splenic Atrophy</th>
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<tbody>
<tr>
<td><strong>CONGENITAL FORMS</strong></td>
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<tr>
<td>Normal and premature neonates</td>
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<td>Isolated congenital hypoplasia</td>
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<td>Ivemark syndrome</td>
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<tr>
<td>Autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia (APECED) syndrome</td>
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<td>Hypoparathyroidism syndrome</td>
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<td>Stormorken syndrome</td>
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<td>Heterotaxia syndromes</td>
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<td><strong>AUTOIMMUNE DISORDERS</strong></td>
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<td>Systemic lupus erythematosus</td>
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<td>Wegener granulomatosis</td>
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<td>Nodous polyarteritis</td>
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<td>Thyroiditis</td>
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<td>Sarcoidosis</td>
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<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
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<td>Coeliac disease</td>
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<td>Inflammatory bowel disease</td>
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<td>Whipple disease</td>
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<tr>
<td>Dermattis herpetiformis</td>
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<td>Intestinal lymphangiectasia</td>
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<td>Idiopathic chronic ulcerative enteritis</td>
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<td><strong>HEPATIC DISORDERS</strong></td>
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<td>Active chronic hepatitis</td>
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<td>Primary biliary cirrhosis</td>
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<td>Hepatic cirrhosis and portal hypertension</td>
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<td>Alcoholism and alcoholic hepatopathy</td>
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<td><strong>INFEKTIOUS DISEASES</strong></td>
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<td>HIV/AIDS</td>
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<td>Pneumococcal meningitis</td>
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<td>Malaria</td>
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<td><strong>ONCOHEMATOLOGIC DISORDERS</strong></td>
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<td>Hemoglobin S diseases</td>
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<td>Bone marrow transplantation</td>
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<td>Chronic graft-versus-host disease</td>
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<td>Acute leukemia</td>
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<td>Chronic myeloproliferative disorders</td>
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<td>Fanconi syndrome</td>
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<td>Splenic tumors</td>
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<td>Mastocytosis</td>
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<td><strong>ALTERATION IN SPLENIC CIRCULATION</strong></td>
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<tr>
<td>Thrombosis of splenic artery</td>
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<td>Thrombosis of splenic vein</td>
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<td>Thrombosis of coeliac artery</td>
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<tr>
<td><strong>AMYLOIDOSIS</strong></td>
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<tr>
<td><strong>MISCELLANEOUS</strong></td>
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</table>

Cells dependent on spleen for survival.

Diagnostic Techniques for and Features of Spleen Dysfunction

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin M memory B cells</td>
<td>Cells dependent on spleen for survival. Produced in marginal zone</td>
</tr>
<tr>
<td>Technetium-99m–labeled sulphur colloidal scintiscan</td>
<td>Quantitation of splenic uptake of colloidal sulphur particles enables a fairly accurate static assessment of spleen function</td>
</tr>
<tr>
<td>Technetium-99m–labeled or rubidium-81–labeled heat-damaged autologous erythrocyte clearance</td>
<td>Measurement of clearance time allows a dynamic evaluation of spleen function</td>
</tr>
<tr>
<td>Detection of Howell-Jolly bodies by staining</td>
<td>Erythrocytes with nuclear remnants</td>
</tr>
<tr>
<td>Detection of pitted erythrocytes by phase-interference microscopy</td>
<td>Erythrocytes with membrane indentations (4% upper limit of the normal range)</td>
</tr>
</tbody>
</table>


RBC transfusion requirements should be minimal (<25 mL/kg/48 hr). These patients are usually hospitalized for 10-14 days and have their activities restricted for months. Laparotomy, with or without splenectomy, is indicated for more marked abdominal bleeding, in patients who have clinical instability or deterioration, or when other organ damage is suspected. Partial splenectomy and splenic repair should be substituted for total splenectomy when feasible to maintain some splenic immune function.

**Splenectomy**

Splenectomy should be limited to specific indications where medical therapy is (or has been) ineffective. These include traumatic splenic rupture, anatomic defects, severe transfusion dependent hemolytic anemia, immune cytopenias, metabolic storage diseases, and secondary hypersplenism. The major long-term risk of splenectomy is sudden, overwhelming postsplenectomy infections (sepsis or meningitis). This risk is especially high in children younger than 5 yr at the time of surgery. The risk of sepsis is less when splenectomy is performed for trauma, RBC membrane defects, and immune thrombocytopenia (2-4%) than when there is sickle cell anemia, thalassemia, or a preexisting immune deficiency (Wiskott-Aldrich syndrome, Hodgkin disease) or reticuloendothelial blockade (storage disease, severe hemolytic anemia) (8-30%). The overall risk is 2-5 per 1,000 asplenic patient years, with a lifelong risk of overwhelming postsplenectomy infections of 5%; more than half occur within 2 yr after splenectomy, although the risk remains lifelong. The use of laparoscopic splenectomy has decreased surgical morbidity and hospitalization time.

Encapsulated bacteria, such as *Streptococcus pneumoniae* (>60% of cases), *Haemophilus influenzae*, and *Neisseria meningitidis*, account for >80% of cases of postsplenectomy sepsis. Because the spleen is responsible for filtering the blood and for early antibody responses, sepsis (with or without meningitis) can progress rapidly, leading to death within 12-24 hr of onset. Febrile splenectomized patients should be evaluated and treated promptly with antibiotics to cover the organisms previously mentioned. This treatment should be initiated at home if access to definitive medical care will be delayed. A broad-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended until specific antibiotic susceptibility and presence or absence of meningitis is known. Vancomycin (to cover penicillin-resistant pneumococci) should be initiated, depending on the illness severity and susceptibilities of pneumococci at the institution. Splenectomized patients are also at increased risk for contracting protozoal infections, such as malaria and babesiosis. Serious infection may occur after an animal bite (particularly dogs) and is due to *Capnocytophaga canimorsus* or *C. cynodegmi*. Prophylactic antibiotics should be given after a bite to potentially prevent sepsis caused by these organisms (see Chapter 724).

Preoperative, intraoperative, and postoperative management may decrease the risk of postsplenectomy infection. It is important to be certain of the need for splenectomy and, if possible, to postpone the operation until the patient is 5 yr of age or older. Pneumococcal, meningococcal, and *H. influenzae* conjugate vaccines given at least 14 days before splenectomy may reduce postsplenectomy sepsis. The 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7) was replaced with the 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13). Thus, depending on what primary pneumococcal vaccine was given, a single dose of PCV13 may be recommended. In addition, the 23-valent pneumococcal polysaccharide vaccine (Pneumovax) should be given at age ≥2 yr and a second dose 5 yr later. Yearly influenza vaccine should also be given as influenza infection is a risk factor for secondary pneumococcal infections. Prophylaxis with oral penicillin VK (125 mg twice daily for children younger than 5 yr; 250 mg twice daily for children 5 yr or older) should be given until at least 5 yr of age and for at least 2 yr after splenectomy. Although the greatest risk is in the immediate postoperative period, reports of deaths occurring years after splenectomy suggest that the risk (and the need for prophylaxis) may be lifelong. Lifelong prophylaxis should be strongly considered in patients who have had an invasive pneumococcal infection or who have an underlying immune deficiency. In children with sickle cell disease, penicillin prophylaxis should be started as soon as the diagnosis is made.
Prophylaxis may be continued into adulthood for higher-risk patients, including those with a history of pneumococcal sepsis, but effectiveness in this older group has not been well documented.

In patients with traumatic injury, splenic repair or partial splenectomy should be considered in an attempt to preserve splenic function. Partial splenectomy or partial splenic embolization may be sufficient to ameliorate some forms of hemolytic anemia. Up to 50% of children whose spleen is removed because of trauma have spontaneous splenosis; surgical splenosis (distributing small pieces of spleen throughout the abdomen) may decrease the risk of sepsis in patients whose splenectomy is necessitated by trauma. However, in both of these settings, the splenic tissue that regrows frequently has poor function.

In addition to postsplenectomy sepsis, splenectomized patients may be at risk for thromboembolic complications, including arterial and venous thrombosis and pulmonary hypertension. These findings have been reported regardless of the underlying reason for splenectomy and the postsplenectomy platelet count. Proposed mechanisms include loss of filtering function of the spleen, allowing abnormal RBCs to remain in the circulation and activate the coagulation cascade. Portal vein thrombosis has been reported as a complication of laparoscopic splenectomy.

Bibliography is available at Expert Consult.
Anatomy and Function of the Lymphatic System

Richard L. Tower and Bruce M. Camitta

The lymphatic system participates in many biologic processes, including fluid homeostasis, absorption of dietary fat, and initiation of specific immune responses. This system includes circulating lymphocytes, lymphatic vessels, lymph nodes, spleen, tonsils, adenoids, Peyer patches, and thymus. Lymph, an ultrafiltrate of blood, is collected by lymphatic capillaries that are present in all organs except the brain, bone marrow, retina, cartilage, epidermis, hair, and nails. These join to form progressively larger vessels that drain regions of the body. The lymphatic vessels carry lymph to the lymph nodes, where it is filtered through sinuses, particulate matter and infectious organisms are phagocytosed, and antigens are presented to surrounding lymphocytes. These actions stimulate antibody production, T-cell responses, and cytokine secretion (see Chapter 123). Lymph is ultimately returned to the intravascular circulation.

The composition of lymph can vary with the site of lymph drainage. It is usually clear, but lymph drained from the intestinal tract may be milky (chylous) because of the presence of fats. The protein content is intermediate between that of an exudate and a transudate. The protein level may be increased with inflammation and in lymph drained from the liver or intestines. Lymph also contains variable numbers of lymphocytes and antigen-presenting cells.

Embryonic lymphatic development (primary lymphangiogenesis) proceeds from the stage of lymphatic competence, through lymphatic commitment, specification, coalescence, and maturation. Secondary lymphangiogenesis occurs in the settings of wound healing and inflammation. Many genes are crucial to normal lymphatic development and function, including Proxl, vascular endothelial growth factor–C (VEGF-C), and vascular endothelial growth factor receptor–3 (VEGFR-3).

Bibliography is available at Expert Consult.
Bibliography
Abnormalities of the lymph vessels may be congenital or acquired. Signs and symptoms result from increased lymphatic tissue mass or from leakage of lymph. **Lymphangiectasia** is dilation of the lymphatics. Pulmonary lymphangiectasia causes respiratory distress (see Chapter 395.6). Involvement of the intestinal lymphatics causes hypoproteinemina and lymphocytopenia secondary to loss of lymph into the intestines (see Chapter 338). Therapy includes minimizing the hydrostatic pressure in the lymphatic system. Reducing dietary intake of long-chain fatty acids and substituting medium-chain triglycerides may accomplish this goal. If unsuccessful, octreotide or propranolol may be tried. **Lymphangioma** is a congenital lymphatic malformation, usually detected by age 2 yr. **Lymphangioma circumscriptum** is defined as the presence of many small, superficial lymphangiomas. Deeper lymphangiomas are classified as either **cavernous lymphangiomas** or **cystic hygromas**. **Lymphangiomatosis** is the presence of multiple or disseminated malformations. Some of these lesions also have a hemangiomatous component (see Chapter 505). Thoracic lymphangiomatosis presents with chylothorax, a mass, or with pulmonary infiltrates. Associated features include bone, skin, and splenic lesions. The disorder is either diffuse or multifocal and is differentiated from lymphangiectasia by the presence of complex anastomosis of vessels with dilation rather than simple dilation of preexisting lymphatic capillaries. Emergent surgical treatment is infrequently necessary due to mass effects. Most lesions may be observed for 18–24 mo to assess for involution. Surgery is effective for superficial lesions, but there is a high incidence of recurrence when used for deeper lesions. Intraliesional sclerosing with OK-432, a streptococcal derivative, has been used successfully in selected patients. Other sclerotherapy agents include pure ethanol and bleomycin. Macrocystic lesions appear to respond better than microcystic lymphangiomas to sclerotherapy. Radiofrequency ablation has been used for lymphatic lesions of the tongue. **Lymphatic dysplasia** may cause multisystem problems. These include lymphedema, chylous ascites, chylorhorax, and lymphangiomias of the bone, lung, or other sites. **Lymphangioleiomyomatosis** is characterized by proliferation of lymphatic endothelial cells and smooth muscle cells in the lungs, leading to airway and lymphatic obstruction, cyst formation, pneumothorax, and respiratory failure. It may initially be mistaken for asthma. Lymphangioleiomyomatosis occurs in young women and is also associated with mutations in the tuberous sclerosis tumor-suppressor gene TSC2 in one-third of cases. Sirolimus (rapamycin) stabilizes lung function, reduces symptoms, and improves life quality; lung transplantation may be required. **Lymphedema**, a localized swelling caused by impaired lymphatic flow, can be congenital or acquired. Congenital lymphedema may be found in Turner syndrome, Noonan syndrome, and the autosomal dominantly inherited Milroy disease, among other chromosomal abnormalities. Several families with Milroy disease have mutations in the vascular endothelial growth factor receptor-3 gene (VEGFR-3).
Autosomal recessive and X-linked inheritance has also been reported. Mutations in \( GJC2 \) are associated with hereditary lymphedema. **Lymphedema praecox** (Meige disease) causes progressive lower extremity edema, usually in females during the peripubertal period or pregnancy. **Hypotrichosis-lymphedema-telangiectasia syndrome**, which has dominant and recessive inheritance patterns, has been linked to mutations in \( SOX18 \). Lymphedema has also been found in association with intestinal lymphangiectasia, cerebrovascular malformation, ptosis, yellow dystrophic nails, distichiasis, and cholestasis. Mutations in \( FOXC2 \) are associated with lymphedema-distichiasis syndrome, which has a pubertal onset of lymphedema. Mutations in \( CCBE1, PTPN14, \) and \( GATA2 \) are associated with Hennekam lymphangiectasia-lymphedema syndrome (lymphedema of the extremities, intestinal lymphangiectasia, mental retardation), lymphedema-choanal atresia syndrome, and Emberger syndrome (lymphedema of the lower extremities and genitalia, deafness, immune dysfunction, and warts), respectively.

Acquired obstruction of the lymphatics can result from tumor, post-irradiation fibrosis, and postinflammatory scarring. **Filariasi** is an important cause of lymphedema in Africa, Asia, and Latin America; of the estimated 120 million infected persons, approximately 40 million (primarily older adolescents and adults) are believed to have lymphedema or hydrocele. Injury to the major lymphatic vessels can cause collection of lymph fluid in the abdomen (chylous ascites) or chest (chylothorax). Untreated lymphedema can be disabling and is associated with immune dysfunction, inflammation, fibrosis, adipose tissue overgrowth, and **lymphangiosarcoma**. Current treatment modalities attempt to reduce localized swelling through massage, exercise, and compression. No drugs have been proven efficacious. Diuretic use should be avoided. The recently discovered gene mutations provide potential for targeted therapy, including gene therapy. Autologous lymph node transplantation and use of growth factors to stimulate lymphangiogenesis may also be on the horizon for treatment of lymphedema.

**Lymphangitis** is an inflammation of the lymphatics that drain an area of infection. Tender, erythematous streaks extend proximally from the infected area. Regional nodes may also be tender. Group A streptococci and \( Staphylococcus aureus \) are the most frequent pathogens and therapy should include antibiotics that treat these organisms.

*Bibliography is available at Expert Consult.*
Bibliography
Palpable lymph nodes are common in pediatrics. Lymph node enlargement is caused by proliferation of normal lymphoid elements or by infiltration with malignant or phagocytic cells. In most patients, a careful history and a complete physical examination suggest the proper diagnosis.

**DIAGNOSIS**

Is the mass a lymph node? Nonlymphoid masses (cervical rib, thyroglossal cyst, branchial cleft cyst or infected sinus, cystic hygroma, goiter, sternomastoid muscle tumor, thyroiditis, thyroid abscess, neurofibroma) occur frequently in the neck and less often in other areas. Is the node enlarged? Lymph nodes are not usually palpable in the newborn. With antigenic exposure, lymphoid tissue increases in volume. They are not considered enlarged until their diameter exceeds 1 cm for cervical and axillary nodes and 1.5 cm for inguinal nodes. Other lymph nodes usually are not palpable or visualized with plain radiographs. What are the characteristics of the node? Acutely infected nodes are usually tender. There may also be erythema and warmth of the overlying skin. Fluctuance suggests abscess formation. Tuberculous nodes may be matted. With chronic infection, many of these signs are not present. Tumor-bearing nodes are usually firm and nontender and may be matted or fixed to the skin or underlying structures.

Is the lymphadenopathy localized or generalized? Generalized adenopathy (enlargement of >2 noncontiguous node regions) is caused by systemic disease (Table 490-1) and is often accompanied by abnormal physical findings in other systems. In contrast, regional adenopathy is most frequently the result of infection in the involved node and/or its drainage area (Table 490-2). When caused by infectious agents other than bacteria, adenopathy may be characterized by atypical anatomic areas, a prolonged course, a draining sinus, lack of prior pyogenic infection, and unusual clues in the history (cat scratches, tuberculosis exposure, venereal disease). A firm, fixed node should always raise the question of malignancy, regardless of the presence or absence of systemic symptoms or other abnormal physical findings.

**TREATMENT**

Evaluation and treatment of lymphadenopathy is guided by the probable etiologic factor, as determined from the history and physical examination. Many patients with cervical adenopathy have a history compatible with viral infection and need no intervention. If bacterial infection is suspected, antibiotic treatment covering at least streptococci and staphylococci is indicated. Those who do not respond to oral antibiotics, as demonstrated by persistent swelling and fever, require IV antistaphylococcal antibiotics. If there is no response in 1-2 days, or if there are signs of airway obstruction or significant toxicity, ultrasound, CT, or MRI of the neck should be obtained. If pus is present, it may be aspirated, with CT or ultrasound guidance, or if it is extensive, may require incision and drainage. Gram stain and culture of the pus should be obtained. The sizes of involved nodes should be documented before treatment. Failure to decrease in size within 10-14 days also suggests the need for further evaluation. This may include a complete blood cell count.

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**Table 490-1**

<table>
<thead>
<tr>
<th>Differential Diagnosis of Systemic Generalized Lymphadenopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFANT</strong></td>
</tr>
<tr>
<td><strong>COMMON CAUSES</strong></td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>CMV</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td><strong>RARE CAUSES</strong></td>
</tr>
<tr>
<td>Chagas disease (congenital)</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Reticuloendotheliosis</td>
</tr>
<tr>
<td>Lymphoproliferative disease</td>
</tr>
<tr>
<td>Metabolic storage disease</td>
</tr>
<tr>
<td>Histiocytic disorders</td>
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<tr>
<td></td>
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<td></td>
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</tbody>
</table>

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; JIA, juvenile idiopathic arthritis (as Still disease); SLE, systemic lupus erythematosus.

Table 490-2 Sites of Local Lymphadenopathy and Associated Diseases

<table>
<thead>
<tr>
<th>CERVICAL</th>
<th>Oropharyngeal infection (viral or group A streptococcal, staphylococcal)</th>
<th>Scalp infection/infestation (head lice)</th>
<th>Mycobacterial lymphadenitis (tuberculosis and nontuberculobus mycobacteria)</th>
<th>Viral infection (EBV, CMV, HHV-6)</th>
<th>Cat-scratch disease</th>
<th>Toxoplasmosis</th>
<th>Kawasaki disease</th>
<th>Thyroid disease</th>
<th>Kikuchi disease</th>
<th>Sinus histiocytosis (Rosai-Dorfman disease)</th>
<th>Autoimmune lymphoproliferative disease</th>
<th>Periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy (PFAPA) syndrome</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ANTERIOR AURICULAR</th>
<th>Conjunctivitis</th>
<th>Other eye infection</th>
<th>Oculoglandular tulariaemia</th>
<th>Facial cellulitis</th>
<th>Otitis media</th>
<th>Viral infection (especially rubella, parvovirus)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>SUPRACLAVICULAR</th>
<th>Malignancy or infection in the mediastinum (right)</th>
<th>Metastatic malignancy from the abdomen (left)</th>
<th>Lymphoma</th>
<th>Tuberculosis</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>EPITROCHLEAR</th>
<th>Hand infection, arm infection*</th>
<th>Lymphoma†</th>
<th>Sarcoïd</th>
<th>Syphilis</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>INGUINAL</th>
<th>Urinary tract infection</th>
<th>Venereal disease (especially syphilis or lymphogranuloma venereum)</th>
<th>Other perineal infections</th>
<th>Lower extremity suppurative infection</th>
<th>Plague</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>HILAR (NOT PALPABLE, FOUND ON CHEST RADIOGRAPH OR CT)</th>
<th>Tuberculosis†</th>
<th>Histoplasmosis†</th>
<th>Blastomycosis†</th>
<th>Coccidioidomycosis†</th>
<th>Leukemia/lymphoma†</th>
<th>Hodgkin disease†</th>
<th>Metastatic malignancy*</th>
<th>Sarcoïdosis†</th>
<th>Castleman disease</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>AXILLARY</th>
<th>Cat-scratch disease</th>
<th>Arm or chest wall infection</th>
<th>Malignancy of chest wall</th>
<th>Leukemia/lymphoma</th>
<th>Brucellosis</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ABDOMINAL</th>
<th>Malignancies</th>
<th>Mesenteric adenitis (measles, tuberculosis, Yersinia, group A streptococcus)</th>
</tr>
</thead>
</table>

*Unilateral.
†Bilateral.
CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6.

count with differential; Epstein-Barr virus, cytomegalovirus, Toxoplasma, and cat-scratch disease titers; antimetabolites O or anti-DNase serologic tests; tuberculin skin test; and chest radiograph. If these are not diagnostic, consultation with an infectious disease or oncology specialist may be helpful. Biopsy should be considered if there is persistent or unexplained fever, weight loss, night sweats, supravacular location, mediastinal mass, hard nodes, or fixation of the nodes to surrounding tissues. Biopsy may also be indicated if there is an increase in size over baseline in 2 wk, no decrease in size in 4-6 wk, or no regression to “normal” in 8-12 wk, or if new signs and symptoms develop.

Differentiating benign disorders from a malignancy may initially be difficult. Hard, nontender, nonerythematous nodes involving multiple regions (including mediastinum and abdomen), hepatic or splenic enlargement, fever, night sweats, and weight loss suggest malignancy or a granulomatous process. Persistence of symptoms and lymphadenopathy greater than 2 wk and certain locations (supravacular, mediastinal, abdomen) also suggest malignancy. Cytopenias and elevated blood lactate dehydrogenase are associated with malignancy and certain inflammatory disorders. CT imaging is helpful in identifying other affected nodes and organs; CT or ultrasonographic guided biopsy is helpful in determining the etiology. Fine needle aspiration or excisional biopsy may be needed for superficial nodes to determine a diagnosis.

Bibliography is available at Expert Consult.

490.1 Kikuchi-Fujimoto Disease (Histiocytic Necrotizing Lymphadenitis)

Richard L. Tower and Bruce M. Camitta

Kikuchi-Fujimoto disease is a rare, usually self-limiting disease that was originally reported in patients of Asian heritage. Cases are now described in all ethnic groups. Familial cases have been reported. Presentation is varied and may include fever of unknown origin, but more often, it occurs in children 8–16 yr of age as firm unilateral posterior cervical adenitis, fever, malaise, elevated erythrocyte sedimentation rate, atypical lymphocytosis, and leukopenia. Nodes range in size from only 0.5–6.0 cm, are painful or tender in only 50% of cases, may be multiple, and must be differentiated from lymphoma. Node involvement may occasionally be bilateral or present in axillary or supravacular nodes.

The etiology is unknown, although viral and bacterial causes have been suggested. Growing evidence supports an abnormal immune response; the diagnosis is made by lymph node biopsy. Histologic features include necrosis with karyorrhexis, a histiocytic infiltrate, crescentic plasmacytoid monocytes and an absence of neutrophils. The disease is self-limiting and usually spontaneously resolves within 6 mo, although relapses have occurred up to 16 yr later. Therapy with systemic steroids is reserved for cases with severe symptoms. Rarely, the disease has been fatal. Many autoimmune diseases have been associated with Kikuchi-Fujimoto disease, most commonly systemic lupus erythematosus. The differential diagnosis includes lymphoma, tuberculous, and systemic lupus erythematosus.

Bibliography is available at Expert Consult.

490.2 Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease)

Richard L. Tower and Bruce M. Camitta

This uncommon, benign, and usually self-limited disease has a worldwide distribution but is more common in Africa and the Caribbean. The etiology is unknown, but immune dysfunction is suspected. Patients present with massive bilateral, painless, mobile cervical adenopathy, along with fever, leukocytosis, high erythrocyte sedimentation
Bibliography


rate, and polyclonal elevation of immunoglobulin G (hypergamma-globulinemia). Night sweats and weight loss are common. Autoimmune hemolytic anemia is an uncommon associated finding. It rarely occurs at birth or in siblings, and males are affected more often than females.

Other nodal chains may be involved. Extranodal involvement occurs in 40% of cases. Soft-tissue involvement of all organ systems has been reported. The most common sites are the skin, followed by the nasal cavity and sinuses, palate, orbit, bone, and central nervous system. Occasionally autoantibodies to erythrocytes or synovium may be present. A biopsy that demonstrates pale histiocytes containing engulfed lymphocytes (emperipolesis), and immunoreactivity to S100 protein in large histiocytes, in conjunction with expected clinical features, is diagnostic. The differential diagnosis includes Langerhans cell histiocytosis, myeloproliferative disorders, and lymphoma.

Therapy is usually not needed for this self-limited disease. However, the disease may recur frequently for many years. Life- or organ-threatening disease or exacerbations may respond to prednisone. Refractory cases have been treated with surgical excision or radiation. Rare patients have been treated with immune-modulating therapy, including interferon-α, 2-chlorodeoxyadenosine, imatinib, and rituximab. Therapy with antibiotics and chemotherapy has been unsuccessful.

Bibliography is available at Expert Consult.

490.3 Castleman Disease
Richard L. Tower and Bruce M. Camitta

Castleman disease is an uncommon lymphoproliferative disease and is also called angiofollicular lymph node hyperplasia. The underlying etiology is unknown, although an association with human herpesvirus 8 has been identified. Human herpesvirus 8 may stimulate excessive production of interleukin 6 (IL-6). The disease usually presents in adolescents or young adults. Enlargement of a single node, most often in the mediastinum or abdomen, is the most common localized presentation. Some patients may have fever, night sweats, weight loss, and fatigue. Management includes surgery and/or radiation therapy.

Multicentric Castleman disease is a systemic lymphoproliferative disorder that causes lymphadenopathy, hepatosplenomegaly, fever, anemia, overexpression of IL-6, and polyclonal hypergammaglobulinemia. Multicentric Castleman disease may be associated with HIV infection, autoimmune disease–associated lymphadenopathy, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-proteins, and skin lesions). Non-Hodgkin lymphoma may be concurrent or may develop as a result of disease progression. There is no standard treatment for multicentric Castleman disease. Therapeutic options include chemotherapy, steroids, monoclonal antibodies to CD20 (rituximab), monoclonal antibodies (siltuximab) to IL-6, anti-IL-6–receptor antibodies (tocilizumab), antiviral agents, and interferon-α. Chemotherapy regimens used for diffuse large B-cell lymphoma and/or rituximab is currently the most common frontline therapies and has achieved durable remissions. Ganciclovir is the most active antiviral agent. Steroids and anti-IL-6 therapies provide symptomatic relief, but symptoms return after stopping therapy.

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


Cancer in patients younger than 20 yr of age is uncommon, with an age-adjusted annual incidence of 18.7 per 100,000 children ages 0-19 yr, representing only approximately 1% of all new cancer cases in a year in the United States or an estimated 16,600 new cases/yr in 2014. This translates to nearly a 1 in 300 chance of developing cancer by age 20 yr. Although the relative 5 yr survival rates have improved from 61% in 1977 to 83.6% in 2010 in all age groups 0-19 yr (Fig. 491-1), malignant neoplasms remain the leading cause of disease-related (noninjury) mortality (12%) among persons 1-19 yr of age with 1,800-1,900 cancer-related deaths annually in the United States among children and adolescents 0-19 yr of age. The relative contribution of cancer to the overall mortality in infants 0-1 yr old and adolescents 15-19 yr old is lower than for children ages 1-14 yr. The impressive improvements in survival over the past 3.5 decades are attributed primarily to advances in treatment and enrollment in clinical trials for the majority of patients. Multinstitutional cooperative clinical trials investigating novel therapies and investigating ways to improve survival rates even further and to decrease treatment-related long-term complications are ongoing. Because increasingly more patients survive their disease, clinical investigations also are focusing on the quality of life among survivors and the late outcomes of therapy for pediatric and adult survivors of childhood cancer. The National Cancer Institute estimates that in 2010 there were 380,000 persons alive (in all age groups) who had survived childhood cancer, corresponding to 1 in 810 of persons younger than 20 yr of age and 1 in 1,000 persons 20-39 yr of age in the U.S. population.

Pediatric malignancies differ markedly from adult malignancies in both prognosis and distribution by histology and tumor site. Lymphohematopoietic cancers (i.e., acute lymphoblastic leukemia, myeloid leukemia, Hodgkin and non-Hodgkin lymphomas) account for approximately 40%, central nervous system cancers for approximately 30%, and embryonal tumors and sarcomas for approximately 10% among the broad categories of childhood cancers (Table 491-1). In contrast, epithelial tumors of organs such as lung, colon, breast, and prostate, which are commonly seen among adults, are rare malignancies in children. Incidence patterns in the pediatric age group show 2 peaks: the first in early childhood and the second in adolescence (Fig. 491-2). During the 1st yr of life, embryonal tumors such as neuroblastoma, nephroblastoma (Wilms tumor), retinoblastoma, rhabdomyosarcoma, hepatoblastoma, and medulloblastoma are most common (Figs. 491-3 and 491-4). These tumors are much less common in older children and adults after cell differentiation processes have slowed considerably. Embryonal tumors, acute leukemias, non-Hodgkin lymphomas, and gliomas peak in incidence from 2-5 yr of age. As children age, bone malignancies, Hodgkin disease, gonadal germ cell malignancies (testicular and ovarian carcinomas), and other carcinomas increase in incidence. Adolescence is a transitional period between the common early childhood malignancies and characteristic carcinomas of adulthood (Fig. 491-4). Incidence rates also vary by gender (generally higher in boys vs girls), race/ethnicity (more common in whites), and between countries (data assembled by the International Agency for Research in Cancer in Lyon, France, http://www.iarc.fr/). Over the past 35 yr, 1975-2010, there has been some increase in the incidence of children and adolescents diagnosed with cancer particularly in occurrence of leukemia and among adolescents. These variations are not fully understood but likely reflect differences in genetic susceptibility and environmental exposures related to both known and unknown causes and risk factors for cancer (Table 491-2).

Childhood cancer includes a diverse array of malignant tumors, termed “cancers,” and nonmalignant tumors arising from disorders of genetic processes involved in control of cellular growth and development. Although many genetic conditions are associated with increased risks for childhood cancer, such conditions are believed to account for <5% of all occurrences (see Chapter 492). The most notable genetic conditions that impart susceptibility to childhood cancer are neurofibromatosis types 1 and 2, Down syndrome, Beckwith-Wiedemann syndrome, tuberous sclerosis, von Hippel-Lindau disease, xeroderma pigmentosum, ataxia-telangiectasia, nevus basal cell carcinoma syndrome, and Li-Fraumeni (P53) syndrome. The varying incidence patterns of individual childhood cancers around the world imply additional genetic and epidemiologic risk factors that remain uncharacterized.

Compared with adult epithelial tumors, an extremely small fraction of pediatric cancers appear to be explained by known environmental exposures (see Table 491-2). Ionizing radiation exposure and several chemotherapeutic agents explain only a small number of pediatric cases (see Chapter 718). The association between fetal exposures and pediatric cancer is largely not established, with the exception of maternal diethylstilbestrol intake during pregnancy and subsequent vaginal adenocarcinoma in adolescent daughters. Environmental exposures that have been studied without convincing evidence for a causal role include nonionizing power frequency electromagnetic fields, pesticides, parental occupational chemical exposures, dietary factors, in vitro fertilization, and environmental cigarette smoke. Viruses have been associated with certain pediatric cancers, such as polyomaviruses (BK, JC, SV40) associated with brain cancer and Epstein-Barr virus with non-Hodgkin lymphoma, but the etiologic importance remains unclear. The etiology of cancer in children still is poorly understood, and epidemiology studies demonstrate that the likely mechanisms are multifactorial, possibly resulting from potential interactions between genetic susceptibility traits and environmental exposures. Ongoing studies are investigating the role of polymorphisms of genes encoding enzymes, which function in the activation or metabolism of xenobiotics, protection of cells against oxidative stress, DNA repair, and/or immune modulation.

Curative therapy with chemotherapy, radiation, and/or surgery can adversely affect a child’s development and result in serious long-term medical and psychosocial effects in childhood and adulthood. Potential adverse late effects include subsequent second malignancy, early mortality, infertility, reduced stature, cardiomyopathy, pulmonary fibrosis, osteoporosis, neurocognitive impairment, affective disorders, and altered social functioning. Much has been learned about the incidence of late effects from large multisite cohort studies such as the Childhood Cancer Survivor Study, an ongoing study of medical and psychosocial outcomes in survivors, which has provided data for the development of clinical care guidelines for survivors (http://www.survivorshipguidelines.org).

Given the relative rarity of specific types of childhood cancer and the sophisticated technology and expertise required for diagnosis, treatment, and monitoring of late effects, all children with cancer
Figure 491-1 Five year relative survival rates (%) by year of diagnosis of all cancers in children 19 yr of age or younger. The difference between the periods 1975-1977 and 2004-2010 is statistically significant (p < 0.05). Rates based on follow-up of patients into 2011 from Surveillance, Epidemiology, and End Results (SEER) database. (Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: SEER Cancer Statistics Review, 1975-2011, Section 28. Bethesda, MD, National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2011/, posted to the SEER website, April 2014.)


Figure 491-3 Generalized incidence of the most common types of cancer in children by age. The cumulative incidence of all cancers is shown as a dashed line. (Courtesy of Archie Bleyer, MD.)

Figure 491-4 Surveillance, Epidemiology, and End Results (SEER) incidence rates by International Classification of Childhood Cancer (ICCC) and age group <20 yr. CNS, central nervous system. (Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: SEER Cancer Statistics Review, 1975-2011, Section 29. Bethesda, MD, National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2011/, posted to the SEER website, April 2014.)

Table 491-1 Age-Adjusted Incidence and Survival Rates of Malignant Neoplasms By Tumor Type Among U.S. Children

<table>
<thead>
<tr>
<th>ANNUAL INCIDENCE RATES PER 1 MILLION CHILDREN, 2007-2011</th>
<th>5-YR SURVIVAL (%) AGE ≤19 YR AT DIAGNOSIS, 2004-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age &lt;1 Yr</strong></td>
<td><strong>Age 1-4 Yr</strong></td>
</tr>
<tr>
<td>Leukemia (ALL/AML)</td>
<td>52 (20/19)</td>
</tr>
<tr>
<td>Lymphoma (Hodgkin)</td>
<td>5.5 (—)</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>49</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>51</td>
</tr>
<tr>
<td>Nephroblastoma/Wilms (renal cell carcinoma)</td>
<td>15 (—)</td>
</tr>
<tr>
<td>Bone</td>
<td>—</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>20</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>28</td>
</tr>
<tr>
<td>Hepatoblastoma (hepatic carcinoma)</td>
<td>10 (—)</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>19</td>
</tr>
<tr>
<td>Malignant epithelial cancer</td>
<td>—</td>
</tr>
</tbody>
</table>

Based on the International Classification of Childhood Cancer (ICCC). Rates are per 1,000,000 children and are age-adjusted to the 2000 U.S. standard population.

*Thyroid carcinoma.
†Malignant melanoma.
— Indicates that the rate could not be calculated with <16 cases for the time interval; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CNS, central nervous system.

should be treated with standardized clinical protocols in pediatric clinical research settings whenever possible. Promoting such treatment, the Children's Oncology Group is a multiinstitutional research consortium that facilitates cooperative clinical, biologic, and epidemiologic research in more than 200 affiliated institutions in the United States, Canada, and other countries (http://childrensoncologygroup.org/). Coordinated participation in such research trials has been a major factor in the increased survival for many children with cancer. Such ongoing efforts are critical to better understand the etiology of childhood cancers, improve survival for malignancies with a poor prognosis, and maximize the quality of life for survivors.

**INFLUENCING THE INCIDENCE OF CANCER**

Pediatricians have a unique opportunity to educate children and adolescents, and their parents, regarding means of preventing cancer. There are only a few recognized environmental causes of childhood cancer that can be avoided or counteracted. One example is immunization against hepatitis B, which does decrease the risk of hepatocellular carcinoma in adolescence and adulthood; another is human papillomavirus vaccination, which prevents cervical cancer. Associations between cumulative radiation exposure from common diagnostic radiologic tests such as CT scans and an increased risk of malignancy later in life are of great concern for pediatricians. Guidelines to ensure the safe clinical use of diagnostic imaging are being evaluated (http://www.imagegently.org/). An objective of pediatric medicine is to teach children how to adopt healthy lifestyles to reduce their risk of cancer during adulthood, such as avoiding tobacco, alcohol, high-fat diets, and obesity. The earlier these habits are instilled, the greater the lifelong benefit and the more likely it is to be present and sustained during adulthood.

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


Cancer is a complex of diseases arising from alterations that can occur in a wide variety of genes. Alterations in normal cellular processes such as signal transduction, cell-cycle control, DNA repair, cellular growth and differentiation, translational regulation, senescence, and apoptosis (programmed cell death) can result in a malignant phenotype.

**GENES INVOLVED IN ONCOGENESIS**

Two major classes of genes are implicated in the development of cancer: oncogenes and tumor-suppressor genes. **Protooncogenes** are cellular genes that are important for normal cellular function and code for various proteins, including transcriptional factors, growth factors, and growth factor receptors. These proteins are vital components in the network of signal transduction that regulate cell growth, division, and differentiation. Protooncogenes can be altered to form oncogenes—genes that, when translated, result in the malignant transformation of a cell.

Oncogenes can be divided into 5 different classes based on their mechanisms of action. Changes in any of these normal cellular components can result in uncontrolled cell growth. Some oncogenes code for growth factors that bind to a receptor and stimulate the production of a protein. Other oncogenes code for growth factor receptors. These are proteins on the cell surface. When growth factors bind to a growth factor receptor, they can turn the receptor on or off. Mutational or posttranslational modifications of the receptor can result in a receptor being permanently turned on with consequent unregulated growth. **Signal transducers** or effectors make up another class. Signal transducers are responsible for taking the signal from the cell surface receptor to the cell nucleus. NRAS, as described below, is an example of this class of protein. **Transcription factors** are molecules that bind to specific areas of the DNA and control transcription. MYC, described below, is an example of a transcription factor that results in overstimulation of cell division. The final class of oncogenes interferes with apoptosis. Cells that no longer respond to the signal to die can continue to proliferate.

The 3 main mechanisms by which protooncogenes can be activated include amplification, point mutations, and translocation (Table 492-1). MYC, which codes for a protein that regulates transcription, is an example of a protooncogene that is activated by amplification. Patients with neuroblastoma in which the MYC gene is amplified 10-300-fold have a poorer outcome. Point mutations can also activate protooncogenes. The NRAS protooncogene codes for a guanine nucleotide–binding protein with guanosine triphosphatase activity that is important in signal transduction and is mutated in 25-30% of acute nonlymphocytic leukemias, resulting in a constitutively active protein. The RET protein is a transmembrane tyrosine kinase receptor that is important in signal transduction. A point mutation in the RET gene results in the constitutive activation of a tyrosine kinase, as found in multiple endoplasia syndromes and familial thyroid carcinoma.

The third mechanism by which protooncogenes become activated is by chromosomal translocation. In some leukemias and lymphomas, transcription factor controlling sequences are relocated in front of T-cell receptors or immunoglobulin genes, resulting in unregulated transcription of the genes and leukemogenesis. Chromosomal translocations can also result in fusion genes; transcription of the fusion gene can result in the production of a chimeric protein with new and potentially oncogenic activity. Examples of cancers associated with fusion genes include the childhood solid tumors like Ewing sarcoma [t(11;22)] and alveolar rhabdomyosarcoma [t(2;13) or t(1;13)]. The translocations result in novel proteins that are useful as diagnostic markers. The best-described translocation in leukemia is the Philadelphia chromosome’s t(9;22), which results in the BCR/ABL protein found in chronic myelogenous leukemia. This translocation results in a tyrosine kinase protein that is constitutively activated. In addition, the protein is localized to the cytoplasm instead of the nucleus, exposing the kinase to a new spectrum of substrates.

Alteration in the regulation of tumor-suppressor genes is another mechanism involved in oncogenesis. Tumor-suppressor genes are important regulators of cellular growth and apoptosis. They have been called recessive oncogenes because the inactivation of both alleles of a tumor-suppressor gene is required for expression of a malignant phenotype.

Knudson’s “2-hit” model of cancer development was based on the observation of the behavior of the RB tumor-suppressor gene. In sporadic cases of retinoblastoma, both alleles of the RB gene must be inactivated. However, in familial cases, children inherit an inactivated allele from 1 parent and consequently require the inactivation of the only remaining normal allele. This helps explain why familial cases of retinoblastoma occur earlier in childhood than sporadic cases, because only 1 “hit” is required.

Another major tumor-suppressor protein is P53, which is known as the “guardian of the genome” because it detects the presence of

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**Table 492-1 Oncogene Activators of Pediatric Tumors**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>CHROMOSOME</th>
<th>GENES</th>
<th>PROTEIN FUNCTION</th>
<th>TUMOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal translocation</td>
<td>t(9;22)</td>
<td>BCR-ABL</td>
<td>Chimeric tyrosine kinase</td>
<td>CML, ALL</td>
</tr>
<tr>
<td></td>
<td>t(1;19)</td>
<td>E2A-PBX1</td>
<td>Chimeric transcription factor</td>
<td>Pre-B ALL</td>
</tr>
<tr>
<td></td>
<td>t(14;18)</td>
<td>MYC</td>
<td>Transcription factor</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td></td>
<td>t(15;17)</td>
<td>APL-RARα</td>
<td>Chimeric transcription factor</td>
<td>APL</td>
</tr>
<tr>
<td></td>
<td>11:q23 and others</td>
<td>MLL</td>
<td>Methyl transferase activity</td>
<td>ALL</td>
</tr>
<tr>
<td></td>
<td>t(12;q21)</td>
<td>TEL-AML 1</td>
<td>Chimeric protein</td>
<td>AML</td>
</tr>
<tr>
<td></td>
<td>t(12;13)(q35;q14) or t(11;13)(p36q14)</td>
<td>FKHF-PAX3</td>
<td>Transcription factor</td>
<td>Biphenotypic ALL</td>
</tr>
<tr>
<td></td>
<td>t(11;q22) or t(7;9q22)</td>
<td>EWS-FLI1</td>
<td>Transcription factor</td>
<td>Rhabdomyosarcoma Wilms</td>
</tr>
<tr>
<td>Gene amplification</td>
<td>Amplicon</td>
<td>MYC</td>
<td>Growth factor kinase, tyrosine kinase</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td></td>
<td>Amplicon</td>
<td>EGFR</td>
<td>Tyrosine kinase receptor</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td></td>
<td>Amplicon</td>
<td>Flt3</td>
<td></td>
<td>AML</td>
</tr>
<tr>
<td>Point mutation</td>
<td>1p</td>
<td>NRAS</td>
<td>Guanosine triphosphatase</td>
<td>AML</td>
</tr>
<tr>
<td></td>
<td>10q</td>
<td>RET</td>
<td>Tyrosine kinase</td>
<td>MEN2</td>
</tr>
</tbody>
</table>

ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; APL, acute promyelocytic leukemia; CML, chronic myelogenous leukemia; MEN2, multiple endocrine neoplasia, type 2.
chromosomal damage and prevents the cell from dividing until repairs have been made. In the presence of damage beyond repair, P53 initiates apoptosis and the cell dies. More than 50% of all tumors have abnormal P53 proteins. Mutations in the P53 gene are important in many cancers, including breast, colorectal, lung, esophageal, stomach, ovarian, and prostatic carcinomas as well as gliomas, sarcomas, and some leukemias.

PTEN (phosphatase and tensin homolog) is one of the most commonly lost tumor suppressors in human cancer. PTEN is a phosphatase that regulates cell-cycle progression. The dephosphorylation of proteins disrupts the Akt/PKB signaling pathway that moderates cell-cycle progression. Loss of PTEN enzyme activity is seen in Proteus, Cowden, and Bannayan-Riley-Ruvalcaba syndromes and in glioblastoma, endometrial carcinoma, and prostate cancer. Decreased phosphatase activity is found in lung and breast cancer. More than 170 putative tumor-suppressor genes are identified.

**SYNDROMES PREDISPOSING TO CANCER**

Several syndromes are associated with an increased risk of developing malignancies, which can be characterized by different mechanisms (Table 492-2). One mechanism involves the inactivation of tumor-suppressor genes such as RB in familial retinoblastoma. Interestingly, patients with retinoblastoma in which 1 of the alleles is inactivated throughout all of the patient's cells are also at a very high risk for developing osteosarcoma. A familial syndrome, Li-Fraumeni syndrome, in which 1 mutant P53 allele is inherited, also has been described in patients who develop sarcomas, leukemias, and cancers of the breast, bone, lung, and brain. Neurofibromatosis is a condition characterized by the proliferation of cells of neural crest origin, leading to neurofibromas. These patients are at a higher risk of developing malignant schwannomas and pheochromocytomas. Neurofibromatosis is often inherited in an autosomal dominant fashion, although 50% of the cases present without a family history and occur secondary to the high rate of spontaneous mutations of the NFI gene.

A second mechanism responsible for an inherited predisposition to develop cancer involves defects in DNA repair. Syndromes associated with an excessive number of broken chromosomes due to repair defects include Bloom syndrome (short stature, photosensitive telangiectatic erythema), ataxia-telangiectasia (childhood ataxia with progressive nervous system and nonneural solid tumors), and Fanconi anemia (short stature, skeletal and renal anomalies, pancytopenia). As a result of the decreased ability to repair chromosomal defects, cells accumulate abnormal DNA that results in significantly increased rates of cancer, especially leukemia. Xeroderma pigmentosum likewise increases the risk of skin cancer, owing to defects in repair to DNA damaged by ultraviolet light. These disorders display an autosomal recessive pattern.

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>TUMOR/CANCER</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHROMOSOMAL SYNDROMES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosome 11p deletion syndrome with sporadic anhidrosis</td>
<td>Wilms tumor</td>
<td>Associated with genitourinary anomalies, mental retardation, WT1 gene</td>
</tr>
<tr>
<td>Chromosome 13q deletion syndrome</td>
<td>Retinoblastoma, sarcoma</td>
<td>Associated with intellectual disability, skeletal malformations; autosomal dominant (bilateral) or sporadic new mutations, RB1 gene</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>Lymphocytic or nonlymphocytic leukemia, especially megakaryocytic leukemia; transient leukemoid reaction</td>
<td>Risk of ALL is increased 20%; risk of AML is increased 400%; patients have an increased sensitivity to chemotherapy</td>
</tr>
<tr>
<td>Klinefelter syndrome (47,XXY)</td>
<td>Breast cancer, extragonadal germ cell tumors</td>
<td>Autosomal dominant; mutations in PTPN11 gene</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>Preleukemia</td>
<td>Recurrent infections may precede neoplasia</td>
</tr>
<tr>
<td>Monosomy 5 or 7</td>
<td>Myelodysplastic syndrome</td>
<td></td>
</tr>
<tr>
<td>CHROMOSOMAL INSTABILITY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>Basal cell and squamous cell carcinomas; melanoma</td>
<td>Autosomal recessive; failure to repair UV-damaged DNA. Mutations in XP gene on chromosome 3p25</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>Leukemia, myelodysplastic syndrome, liver neoplasias, rare head and neck tumors, GI and GU cancers</td>
<td>Autosomal recessive; chromosome fragility; positive diepoxybutane test result. Mutations in FANCX gene family</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>Leukemia, lymphoma, and solid tumors</td>
<td>Autosomal recessive; increased sister chromatid exchange; mutations in BLM gene; member of the RecQ helicase gene</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>Lymphoma, leukemia, less commonly central nervous system and nonneural solid tumors</td>
<td>Autosomal recessive; sensitive to X-irradiation, radiomimetic drugs; mutation in ATM tumor-suppressor gene</td>
</tr>
<tr>
<td>Dysplastic nevus syndrome</td>
<td>Melanoma</td>
<td>Autosomal dominant; some cases associated with mutations in CDKN2A gene</td>
</tr>
<tr>
<td>Rothmund-Thompson syndrome</td>
<td>Osteosarcoma; skin cancers</td>
<td>Autosomal recessive; mutation in RecQ helicase gene family</td>
</tr>
<tr>
<td>Werner syndrome (premature aging)</td>
<td>Soft tissue sarcomas</td>
<td>Autosomal recessive; mutation in the WRN gene; member of the RecQ helicase gene family</td>
</tr>
<tr>
<td>IMMUNODEFICIENCY SYNDROMES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>Lymphoma, leukemia</td>
<td>X-linked recessive; WAS gene mutation (Xp11.22-23); WASP protein functions in signal transduction associated with cytoskeletal actin filament rearrangement</td>
</tr>
<tr>
<td>X-linked immunodeficiency (Duncan syndrome)</td>
<td>Lymphoproliferative disorder</td>
<td>X-linked; Epstein-Barr viral infection can result in fatal outcome; mutation in SH2D1A gene locus</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia (Bruton disease)</td>
<td>Lymphoma, leukemia</td>
<td>X-linked; mutation in BTK gene resulting in absence of mature B cells</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>Leukemia, lymphoma</td>
<td>X-linked; mutations in ADA gene</td>
</tr>
<tr>
<td>DISORDER</td>
<td>TUMOR/CANCER</td>
<td>COMMENT</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neurofibromatosis 1</td>
<td>Neurofibroma, optic glioma, acoustic neuroma, astrocytoma, meningioma,</td>
<td>Autosomal dominant; mutation in tumor-suppressor gene, NF1</td>
</tr>
<tr>
<td>Neurofibromatosis 2</td>
<td>Bilateral acoustic neuromas, meningiomas</td>
<td>Autosomal dominant; mutation in tumor-suppressor gene, NF2</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Fibroangiomaticus nevi, myocardial rhabdomyoma</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Gorlin-Goltz syndrome (nevus basal cell carcinoma syndrome)</td>
<td>Multiple basal cell carcinomas; medulloblastoma</td>
<td>Autosomal dominant; mutation in PTCH gene</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Bone, soft tissue sarcoma, breast</td>
<td>Mutation of PS3 tumor-suppressor gene, autosomal dominant</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Sarcoma</td>
<td>Autosomal recessive; increased risk of secondary malignancy 10-20 yr later; mutation in RB tumor-suppressor gene</td>
</tr>
<tr>
<td>Hemihypertrophy ± Beckwith syndrome</td>
<td>Wilms tumor, hepatoblastoma, adrenal carcinoma</td>
<td>WTI gene; 25% develop tumor, most in 1st 5 yr of life</td>
</tr>
<tr>
<td>von Hippel-Landau disease</td>
<td>Hemangioblastoma of the cerebellum and retina, pheochromocytoma, renal cancer</td>
<td>Autosomal dominant; mutation in tumor-suppressor gene, VHL gene</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia syndrome, type 1 (Wermer syndrome)</td>
<td>Parathyroid, pancreatic islet, and pituitary tumors</td>
<td>Autosomal dominant; mutation in PYGM tumor-suppressor gene</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia syndrome, type 2A (Sipple syndrome)</td>
<td>Medullary carcinoma of the thyroid, hyperparathyroidism, pheochromocytoma</td>
<td>Autosomal dominant; mutations in CYS-rich regions of the RET gene activate this protooncogene; RET codes for a tyrosine kinase; monitor calcitonin and calcium levels</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2B (multiple mucosal neuroma syndrome)</td>
<td>Mucosal neuma, pheochromocytoma, medullary thyroid carcinoma, Marfan habitus; neuropathy</td>
<td>Autosomal dominant; mutation in catalytic site (codon 883 or 914) activates protooncogene; RET codes for a tyrosine kinase</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Colorectal, thyroid carcinoma, duodenal and periampullar carcinomas; pediatric hepatoblastoma</td>
<td>Autosomal dominant; mutation in SMAD4 gene</td>
</tr>
<tr>
<td>Familial juvenile polyposis</td>
<td>Colorectal carcinoma</td>
<td>Autosomal dominant; mutation in mismatch repair genes; hMSH2, hMLH1, PMS1, PMS2, hMSh6, hMSh3</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer (Lynch syndrome, NHPCC)</td>
<td>Colon cancer</td>
<td>Autosomal dominant; APC gene</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>Pediatric brain tumors and increased risk of colon carcinoma and polyps</td>
<td>Autosomal dominant, APC gene</td>
</tr>
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<td>Familial adenomatous polyposis coli</td>
<td>Adenocarcinoma of colon</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Gardner syndrome</td>
<td>Adenocarcinoma of colon, skull and soft tissue tumors</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>Gastrointestinal carcinoma, ovarian neoplasia</td>
<td>Autosomal dominant; LKB1 gene codes for a Ser/Thr kinase that regulates cell cycle, metabolism, cell polarity</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Hepatocellular carcinoma</td>
<td>Autosomal dominant; malignancy associated with cirrhotic liver</td>
</tr>
<tr>
<td>Glycogen storage disease 1 (von Gierke disease)</td>
<td>Hepatocellular carcinoma</td>
<td>Autosomal recessive; malignancy associated with cirrhotic liver</td>
</tr>
<tr>
<td>Tyrosinemia, galactosemia</td>
<td>Hepatocellular carcinoma</td>
<td>Mutation in glucose-6-phosphatase or glucose-6-phosphatase translocase genes</td>
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<td>BRCA1 and BRCA2</td>
<td>Breast, ovarian</td>
<td>Autosomal recessive; tumor associated with cirrhotic liver</td>
</tr>
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<td>Diamond-Blackfan anemia</td>
<td>AML, myelodysplastic syndrome, osteogenic sarcoma</td>
<td>DNA repair defect</td>
</tr>
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<td>Shwachman-Diamond syndrome</td>
<td>AML, myelodysplasia</td>
<td>Autosomal dominant; family 9 genes encoding ribosomal proteins</td>
</tr>
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<td>Hereditary diffuse gastric cancer</td>
<td>Gastric cancer</td>
<td>Autosomal recessive; SBDS gene; chromosome 7q11.21</td>
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<td>Pleuropulmonary blastoma family tumor and dysplasia (DICER1)</td>
<td>Pulmonary blastoma</td>
<td>Autosomal dominant; CDH1 gene</td>
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<td>Hereditary neuroblastoma</td>
<td>Neuroblastoma</td>
<td>Encoded protein is a ribonuclease required for microRNA processing</td>
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<td>Hereditary paraganglioma–pheochromocytoma syndrome</td>
<td>Paraganglioma</td>
<td>Two genes have been identified:</td>
</tr>
<tr>
<td>Congenital or cyclic neutropenia</td>
<td>Paraganglioma</td>
<td>• Anaplastic lymphoma kinase (ALK) at chromosome 2p23</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytomas</td>
<td>• Paired-like homeobox 2b (PHOX2B) at chromosome 4q12</td>
</tr>
<tr>
<td></td>
<td>Myelodysplastic syndrome</td>
<td>Mutation in the mitochondrial enzyme succinate dehydrogenase protein (SDH)</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>ELANE mutation at 19p13.3; elastase; neutrophil expressed</td>
</tr>
</tbody>
</table>

ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; GI, gastrointestinal; GU, genitourinary; JMML, juvenile myelomonocytic leukemia; NHPCC, nonhereditary polyposis colon cancer.
The third category of inherited cancer predisposition is characterized by defects in immune surveillance. This group includes patients with Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, and the X-linked lymphoproliferative syndrome. The most common types of malignancy in these patients are lymphoma and leukemia. Cure rates for immunodeficient children with cancer are much poorer than for nonimmunodeficient children with similar malignancies, suggesting a role for the immune system in cancer treatment as well as in cancer prevention.

**OTHER FACTORS ASSOCIATED WITH ONCOGENESIS**

**Viruses**

Several viruses have been implicated in the pathogenesis of malignancy. The association of the Epstein-Barr virus (EBV) with Burkitt lymphoma and nasopharyngeal carcinoma was identified more than 30 yr ago, but EBV infection alone is not sufficient for malignant transformation. EBV is also associated with mixed cellularity and lymphocyte-depleted Hodgkin disease, as well as some T-cell lymphomas, which is particularly intriguing because EBV normally does not infect T lymphocytes. The most conclusive evidence for a role of EBV in lymphogenesis is the direct causal role of EBV for B-cell lymphoproliferative disease in immunocompromised persons, especially those with AIDS.

Children who are chronically infected with hepatitis B (hepatitis B surface antigen–positive) have a >200-fold increased risk of developing hepatocellular carcinoma. In adults, the latency period between viral infection and the development of hepatocellular carcinoma approaches 20 yr. However, in children who acquire the viral infection through perinatal transmission, the latency period can be as short as 6–7 yr. The additional factors that are required for the malignant transformation of the virally infected hepatocytes are not clear. Hepatitis C virus infection is another risk factor for hepatocellular carcinoma and is also associated with splenic lymphoma.

Nearly all cervical carcinomas contain human papillomavirus (HPV). High-risk HPVs include types 16 and 18 but also types 31, 33, 35, 45, and 56, which are also commonly found in women without lesions. The low-risk HPVs, including 6 and 11 that are commonly found in genital warts, are almost never associated with malignancies. Like other virus-associated cancers, the presence of HPV alone is not sufficient to cause malignant transformation. The mechanism by which HPV 19 induces malignant transformation is thought to involve P53 and RB tumor-suppressor genes, which regulate the cell cycle by acting as gatekeepers of the G1/S and G2/M checkpoints. By interfering with these proteins, HPV alters the regulation of cell growth.

Human herpesvirus 8 is associated with Kaposi sarcoma, primary effusion B-cell lymphoma, and the plasma cell variant of Castleman disease, all of which occur primarily in persons with AIDS. Human T-cell leukemia virus 1 is associated with adult T-cell leukemia and lymphoma.

**Genomic Imprinting**

The development of cancer has also been linked to genomic imprinting, which is the selective inactivation of 1 of 2 alleles of a certain gene. The inactivated gene is determined by whether the gene is inherited from the mother or father. For example, normally the maternal IGF2 (insulin-like growth factor receptor 2) gene is inactivated. The inactivation is thought to be secondary to methylation of specific CpG sequences upstream of the IGF2 promoter, which interferes with the transcription of the IGF2 gene. In some Wilms tumors, there is loss of methylation in the upstream area of the maternal gene, which, in turn, allows transcript expression of the maternal IGF2 gene. At the same time the H19 gene (whose function is not yet clear), a previously actively transcribed maternal gene, is silenced by methylation. Beckwith-Wiedemann syndrome, an overgrowth syndrome characterized by macrosomia, macroglossia, hemihypertrophy, omphalocele, and renal anomalies, is associated with an increased risk of Wilms tumor, hepatoblastoma, rhabdomyosarcoma, neuroblastoma, and adrenal cortical carcinoma. The increased risk in developing cancer is associated with changes in the methylation pattern of genes on the 11p15 chromosome. Studies indicate that methylation patterns in a given individual change over time and that specific groups of methylation changes tend to cluster within families, suggesting heritability of the pattern of changes.

**Telomerase**

Telomeres are a series of tens to thousands of TTAGGG repeats at the ends of chromosomes that are important for stabilizing the chromosomal ends and limiting breakage, translocation, and loss of DNA material. With DNA replication there is a progressive shortening of telomere length, which is a hallmark of cellular aging and may be a senescence signal. In some instances telomerase, an enzyme that adds telomeres to the ends of chromosomes, becomes active. The addition of telomeres can be found in immortalized cell lines and most tumor types, and as a consequence, these cells might have a survival advantage, allowing them to undergo additional cell divisions. Therapy aimed at inhibiting telomerase activity can result in cell death.

*Bibliography is available at Expert Consult.*
Bibliography

Childhood cancer is uncommon and can manifest with symptoms seen with benign illnesses. The challenge for the pediatrician is to be alert to the clues suggesting a diagnosis of cancer. In addition to the classic manifestations, any persistent, unexplained symptom or sign should be evaluated as potentially emanating from a cancerous or precancerous condition. As part of the diagnostic evaluation, the pediatrician and pediatric oncologist must convey the possible diagnosis to the patient and family in a sensitive and informative manner.

**SIGNS AND SYMPTOMS**

The symptoms and signs of cancer are variable and nonspecific in pediatric patients. The types of cancer that occur during the 1st 20 yr of life vary dramatically as a function of age—more so than at any other comparable age range (see Chapter 491). Unlike cancers in adults, childhood cancers usually originate from the deeper, visceral structures and from the parenchyma of organs rather than from the epithelial layers that line the ducts and glands of organs and compose the skin. In children, dissemination of disease at diagnosis is common, and presenting symptoms or signs are often caused by systemic involvement. Pain was one of the initial presenting symptoms in more than 50% of children with cancer in one study. Infants and young children cannot express or localize their symptoms well. Another factor is the variability in the physiology and biology of the host that are related to growth and development during infancy, childhood, and adolescence.

The signs of cancer in children are often attributed to other causes before the malignancy is recognized. Delays in diagnosis are particularly problematic during late adolescence and are the result of a variety of factors prominent in this age group, including loss of health insurance coverage.

Although there is no clearly established set of warning signs of cancer in young people, the most common cancers in children suggest some guidelines that may be helpful in early recognition of signs and symptoms of cancer (Table 493-1). Most of the symptoms and signs are not specific and might represent other possibilities in a differential diagnosis. Nonetheless, these hints encompass the common cancers of childhood and have been very useful in early detection.
Common Manifestations of Childhood Malignancies

<table>
<thead>
<tr>
<th>SIGNS AND SYMPTOMS</th>
<th>POTENTIAL ETIOLOGY</th>
<th>POSSIBLE ONCOLOGIC DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional/Systemic</td>
<td>Fever, persistent or recurrent infection, neutropenia, fever of unknown origin, weight loss, night sweats, painless lymphadenopathy, hypertension, soft tissue mass</td>
<td>Bone marrow infiltration, lymphoma, lymphoma, metastatic solid tumor, renal or adrenal tumor, local or metastatic tumor</td>
</tr>
<tr>
<td>Neurologic/Ophthalmologic</td>
<td>Headache with emesis, visual disturbances, ataxia, papilledema, cranial nerve palsies, leukokoria (white pupil), peri orbital ecchymosis, miosis, ptosis, heterochromia, opsoclonus myoclonus, ataxia, exophthalmos, proptosis, physical examination findings in a child with malignancy are dependent on whether the cancer is systemic (see Table 493-1) or localized.</td>
<td>Increased intracranial pressure, retinal mass, metastasis, Horner syndrome: compression of cervical sympathetic nerves, neurotransmitters? Autoimmunity? Orval tumor, decreased level of consciousness, cranial nerve palsies, ataxia, afebrile seizures, ptosis, decreased visual activity, neuroendocrine deficits, and increased intracranial pressure, which may be diagnosed by the presence of papilledema (Fig. 493-3). Any focal neurologic deficit in the motor or sensory system, especially a decrease in cranial nerve function, should prompt further investigation for malignancy.</td>
</tr>
<tr>
<td>Respiratory/Thoracic</td>
<td>Cough, stridor, pneumonia, tracheal bronchial compression, superior vena cava syndrome, vertebral or nerve root compression, dysphagia, periorbital ecchymosis, petechiae, thrombocytopenia</td>
<td>Anterior mediastinal mass, posterior mediastinal mass</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal mass, diarrhea</td>
<td>Adrenal, renal, or lymphoid tumor, vasoactive intestinal polypeptide</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Pallor, anemia, petechiae, thrombocytopenia, bone marrow infiltration, bone marrow infiltration</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Bone pain, limp, arthralgia, primary bone tumor, metastasis to bone</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes insipidus, galactorrhea, poor growth</td>
<td>Neuroendocrine involvement of hypothalamus or pituitary gland</td>
</tr>
</tbody>
</table>


PHYSICAL EXAMINATION

Physical examination findings in a child with malignancy are dependent on whether the cancer is systemic (see Table 493-1) or localized. The cancers most common in children involve the lymphohematopoietic system. When the bone marrow is compromised by malignancy (e.g., leukemia, disseminated neuroblastoma), typical findings include pallor from anemia; bleeding, petechiae, or purpura from thrombocytopenia or coagulopathy; cellulitis or other localized infection from leukopenia; skin nodules (especially in infants) and hepatosplenomegaly from malignant leukocytosis. Abnormalities found in lymphatic function, should prompt further investigation for malignancy.

Abdominal masses can be divided into upper, middle, and lower locations. Malignancies in the upper abdomen include Wilms tumor, neuroblastoma, hepatoblastoma, germ cell tumors, and sarcomas. Enlargement of the liver or spleen from leukemia can be mistaken for an upper abdominal mass. Midabdominal masses include non-Hodgkin lymphoma, neuroblastoma, germ cell tumors, and sarcomas. Lower abdominal masses include ovarian tumors, germ cell tumors, and sarcomas.

Rhabdomyosarcoma commonly appears as an extremity mass, particularly in adolescents. These tumors can be deceptively benign in appearance, but as with all unexplained masses they require immediate attention. Sacrococcygeal masses in neonates are usually teratomas, which are usually benign but can undergo malignant transformation if not removed promptly. Neuroblastoma can present as “blueberry muffin” spots on the skin of neonates or as periorbital ecchymosis in older children.

Ophthalmologic presentation of malignancy includes a white pupillary reflex (Fig. 493-4) rather than the usual red reflection from...
Figure 493-1 Cervical lymphadenopathy. Manifestations on physical examination (A) and on ultrasound examination (B). N, Abnormally enlarged lymph nodes. (From Sinniah D, D’Angio GJ, Chatten J, et al: Atlas of pediatric oncology, London, 1996, Arnold.)

Figure 493-2 Anterior upper mediastinal mass from non-Hodgkin lymphoma. A, Plain chest X-ray. B, CT scan. C, Positron emission tomography (PET) scan.


incident light. A white pupillary reflex is essentially pathognomonic for retinoblastoma, although some benign conditions can mimic this finding. Proptosis can be produced by rhabdomyosarcoma, neuroblastoma, lymphoma, and Langerhans cell histiocytosis. Horner syndrome, iris heterochromia, and opsoclonus-myoclonus all suggest a diagnosis of neuroblastoma.

**AGE-RELATED MANIFESTATIONS**
Because various types of cancer in children occur at specific ages, the physician should tailor the history and physical examination based on the age of the child. The embryonal tumors, including neuroblastoma, Wilms tumor, retinoblastoma, hepatoblastoma, and rhabdomyosarcoma, usually occur during the 1st 2 yr of life (see Fig. 491-4). From 1-4 yr of age, acute lymphoblastic leukemia peaks in incidence. Brain tumors have a peak incidence in the 1st decade of life. Non-Hodgkin lymphomas are uncommon earlier than 5 yr of age but steadily increase thereafter. During adolescence, bone tumors, Hodgkin disease, and the gonadal and soft tissue sarcomas predominate. Hence, for infants and toddlers, special attention should be paid to the possibility of embryonal and intraabdominal tumors. Preschool-age and early school-age children showing compatible signs and symptoms should be specifically evaluated for leukemia. School-age children might present with lymphoma or with brain tumors. Adolescents require assessment for bone and soft tissue sarcomas and gonadal malignancies, as well as for Hodgkin lymphoma.

**EARLY DETECTION**
The prognosis of malignancy in children depends primarily on tumor type, extent of disease at diagnosis, and rapidity of response to treatment. Early diagnosis helps to ensure that appropriate therapy is given in a timely fashion and hence optimizes the chances of cure. Because most physicians in general practice rarely encounter children with undiagnosed cancer, they should remember to investigate the possibility of malignancy, especially when they encounter an atypical course of a common childhood condition, unusual manifestations that do not fit common conditions, and any persistent symptom that defies diagnosis. Delays in diagnosis are particularly likely in certain clinical situations. The cardinal symptom of both osteosarcoma and Ewing sarcoma is localized and usually persistent pain. Because these tumors occur during the 2nd decade of life, a time of increased physical activity, patients often assume the pain results from trauma. Prompt radiologic evaluation can help confirm the diagnosis. Lymphoma, especially during adolescence, often manifests as an anterior mediastinal mass. Symptoms such as chronic cough, unexplained shortness of breath, or “new-onset asthma” are typical with this presentation and are often overlooked. Tumors of the nasopharynx or middle ear can mimic infection. Prolonged, unexplained ear pain, nasal discharge, retropharyngeal swelling, and trismus should be investigated as possible signs of malignancy.

Early symptoms of leukemia may be limited to prolonged or unexplained low-grade fever or bone and joint pain. Blood counts with abnormalities in two or more cell lines might indicate the need for bone marrow examination, even when leukemic blast cells are not seen in the blood smear (see Table 493-1).

Mass screening for children with malignancy is not feasible. A screening program to detect early-stage neuroblastoma was successful in documenting more cases of the disease, but it had no impact on overall outcome. However, certain children are at increased risk for cancer and require an individualized plan to ensure early detection of malignancy. Selected examples include children with certain chromosome abnormalities, such as Down syndrome, Klinefelter syndrome, WAGR syndrome (Wilms tumor, aniridia, genital abnormalities, and mental retardation); children with overgrowth syndromes, such as Beckwith-Wiedemann syndrome, and hemihypertrophy; children with certain inherited single-gene disorders, including retinoblastoma, P53 mutations (Li-Fraumeni syndrome), familial adenomatous polyposis, and neurofibromatosis (see Table 492-2).

**ENSURING THE DIAGNOSIS**
When a malignant neoplasm is suspected, the immediate goal is to confirm the diagnosis. A tentative diagnosis can often be established on the basis of the patient’s age, symptoms, and location of masses. Selected imaging techniques and tumor markers can facilitate the diagnostic approach (Table 493-2). Especially when a solid tumor is present,
### Work-up of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases—cont’d

<table>
<thead>
<tr>
<th>MALIGNANCY</th>
<th>BONE MARROW ASPIRATE OR BIOPSY</th>
<th>CHEST X-RAY</th>
<th>CT SCAN</th>
<th>MRI</th>
<th>PET SCAN</th>
<th>BONE SCAN</th>
<th>CSF ANALYSIS</th>
<th>SPECIFIC MARKERS</th>
<th>OTHER TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (selected sites)</td>
<td>—</td>
<td>Yes</td>
<td>Yes (for parameningeal tumors only)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>—</td>
<td>Yes</td>
<td>Yes (of chest)</td>
<td>Yes (for primary tumors)</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (of chest)</td>
<td>Yes (for primary tumors)</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Consider MRI of brain</td>
<td>—</td>
<td>—</td>
<td>AFP, HCG</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Liver tumors</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Selected cases</td>
<td>—</td>
<td>Yes</td>
<td>Yes (includes brain)</td>
<td>—</td>
<td>Selected cases</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Table 493-2**  
*Work-up of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases—cont’d*

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**AFP, α-Fetoprotein; CNS, central nervous system; CSF, cerebrospinal fluid; HCG, human chorionic gonadotropin; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; VMA, vanillylmandelic acid.*


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the pediatric oncologist, surgeon, and pathologist should work as a team to determine the site of biopsy, amount of tissue required, and whether fine-needle aspiration, percutaneous image-guided biopsy, incisional biopsy, or excisional biopsy and tumor resection are indicated. For selected situations, at the time of the initial diagnostic procedure, plans for bone marrow aspiration and biopsy and placement of central venous access may be appropriate.

Pathologic evaluation of pediatric malignancies requires appropriate handling of tissue so that multiple different techniques can be used. It is important that fresh tissue not be placed in formalin. Besides routine light microscopy, pathologic evaluation may include immunohistochemistry, flow cytometry, cytogenetics, and molecular genetic studies (fluorescence in situ hybridization, reverse-transcriptase polymerase chain reaction). Emerging technologies include DNA microarray analysis and cancer genome sequencing that can identify specific gene expression patterns and sequences in tumors. In time, these technologies might ensure more accurate classification and treatment.

### STAGING

Once a specific diagnosis is confirmed, studies to define the extent of the malignancy are necessary to determine prognosis and treatment. Table 493-2 outlines the minimum evaluation required for common pediatric malignancies. In addition, for many tumors (e.g., Wilms tumor, neuroblastoma, rhabdomyosarcoma) a surgical staging system is used. Surgical stage can be determined at the time of the initial diagnostic procedure or subsequently. For example, a patient who has abdominal surgery for possible Wilms tumor or neuroblastoma should have careful evaluation and biopsy of all adjacent lymph nodes. A child with rhabdomyosarcoma can require a subsequent biopsy of sentinel lymph nodes as determined by scintigraphy or dye injection adjacent to the primary tumor. The pathologist facilitates staging by examining margins of the specimen to determine residual tumor.

*Bibliography is available at Expert Consult.*
Bibliography


Treatment of children with cancer begins with an absolute requirement for the correct diagnosis (including subtype), proceeds through accurate and thorough staging of the extent of disease and determination of prognostic subgroup, provides appropriate multidisciplinary and usually multimodal therapy, and requires assiduous evaluation of the possibilities of recurrent disease and of adverse late effects of the disease and the therapies rendered. Throughout treatment, every child with cancer should have the benefit of the expertise of specialized teams of providers of pediatric cancer care, including pediatric oncologists, pathologists, radiologists, surgeons, radiotherapists, nurses, and support staff, including nutritionists, social workers, psychologists, pharmacists, other medical specialists, and teachers trained to work with seriously ill children.

The best chance for cure of cancer is during the initial course of treatment; the cure rates for patients with recurrent disease are much lower than those for patients with primary disease. All patients with cancer should be referred to an appropriate specialized center as soon as possible when the diagnosis of cancer is suspected. All such centers in North America are identified on the Children’s Oncology Group website (http://www.childrensoncologygroup.org) and on the National Cancer Institute cancer trials website (http://www.clinicaltrials.gov). The remarkable increases in cure rates for childhood malignancies since the 1970s would not have occurred without the collective participation of patients and their physicians in clinical research programs at these centers. In the United States, the National Cancer Institute’s Clinical Trials Cooperative Groups Program is associated with a >80% reduction in the incidence of mortality from childhood cancer despite an overall increase in cancer incidence during this interval (Fig. 494-1). After what appeared to be a plateau in the rate of decline in mortality in the early 2000s, there is now evidence that the mortality rate
continues to decline. Notably, a greater decline in mortality has been seen in the adolescent and young adult population when compared to children <15 yr old, reversing prior trends (Fig. 494-2). The most current information on treatment of all types of childhood cancer is available in the PDQ (Physician Data Query) on the National Cancer Institute website (http://www.cancer.gov/cancertopics/pdq/pediatrictreatment).

**DIAGNOSIS AND STAGING**

Accurate diagnosis and staging of the extent of disease are imperative, especially for childhood cancers that have high cure rates, because the nature of therapy depends strongly on the type of cancer. In addition, **prognostic subgroups** based on the stage of disease have been established for most cancers that occur in children. Accordingly, children with a better prognosis are treated with less-intensive therapy, including lower doses of chemotherapy or radiation therapy, a shorter duration of treatment, or elimination of at least one treatment modality (radiation therapy, chemotherapy, surgery). Accurate staging thus reduces the risk of excessive acute adverse effects and long-term complications of therapy in patients whose prognosis indicates that less therapy is required for cure. Overtreatment of patients with a more favorable prognosis is a definite risk if the patient is not referred to a therapy is required for cure. Overtreatment of patients with a more favorable prognosis is a definite risk if the patient is not referred to a cancer treatment center for management of adverse effects of such treatment. Conversely, undertreatment also is a clear risk if the diagnosis and stage are not correct, resulting in a compromise of an otherwise high potential for cure.

**Diagnostic imaging** is a critical phase of evaluation in most children with solid tumors (i.e., cancers other than leukemia). MRI, CT, ultrasonography, scintigraphy (nuclear medicine scans), positron emission tomography, and spectroscopy, as appropriate, all serve a clear purpose in the evaluation of children with cancer, not only before treatment to determine the extent of disease and the appropriate therapy but also during follow-up to determine whether the therapy was effective. In addition, response to treatment as determined by imaging techniques is being increasingly used to guide changes in the therapy.

Expertise in pathology and laboratory medicine provides critical diagnostic support and guides therapy in most children with cancer. Relatively noninvasive methods of obtaining tumor tissue (such as fine-needle aspiration and percutaneous image-guided biopsies) can be performed in pediatric centers with appropriate expertise in diagnostic imaging, interventional radiology, cytology, and anesthesia support. Sentinel node mapping is increasingly being applied in the staging of children's cancers. Determining the adequacy of surgery by evaluating frozen sections of the surgical margins for tumor cells is essential in many tumor operations.

**A MULTIMODAL, MULTIDISCIPLINARY APPROACH**

Many pediatric subspecialties are involved in the evaluation, treatment, and management of children with cancer, including provision of primary therapy and supportive care services (Fig. 494-3). More than two of the primary modalities are often used together, with chemotherapy being the most widely used, followed, in order of use, by surgery, radiation therapy, and biologic agent therapy (Fig. 494-4). The leukemias that occur in childhood usually are managed with chemotherapy alone, with a small proportion of patients receiving cranial or craniospinal radiation therapy to prevent or treat overt central nervous system (CNS) leukemia. Children with non-Hodgkin
Chemotherapy is used more widely in children than in adults because children better tolerate the acute adverse effects and the malignant diseases that occur in childhood have a narrow therapeutic index (a low ratio of efficacy to toxicity). The acute and chronic adverse effects of these treatments can be minimized but not entirely avoided.

Biologic agent therapy has become an important modality in a few childhood cancers (see Fig. 494-4). This type of treatment generally refers to immunotherapy, biologic response modifiers, or endogenously occurring molecules that have therapeutic effects in supraphysiologic doses. Examples are retinoic acid therapy in acute promyelocytic leukemia, monoclonal antibody therapy for neuroblastoma and certain non-Hodgkin lymphomas, tyrosine kinase inhibitors such as imatinib mesylate for chronic myelogenous and Philadelphia chromosome-positive leukemias, and radioactive metaiodobenzylguanidine therapy for neuroblastoma.

Chemotherapy is used more widely in children than in adults because children better tolerate the acute adverse effects and the malignant diseases that occur in childhood are more responsive to chemotherapy than are malignant diseases of adults. Radiation therapy is used sparingly in children because they are more vulnerable than adults to its late adverse effects.

Whenever possible, treatment is given on an outpatient basis. Children should remain living at home and in school as much as possible throughout treatment. Increasingly, pediatric cancer therapies are being administered to ambulatory patients, with the advent of such innovations as programmable infusion pumps, oral chemotherapeutic regimens, early discharge from hospital with intensive outpatient support care, and home healthcare services. Some patients miss a considerable amount of school in the 1st yr after diagnosis because of the intensity of therapy or its adverse effects and of the ensuing complications of the disease or therapy. Tutoring should be encouraged so that children do not fall behind in their schooling; counseling should be provided as appropriate. In-hospital school services should be provided for patients who must spend much of their time as inpatients receiving therapy for disease or for managing adverse effects.

Development of selective, highly effective therapy for cancer in both children and adults had been hindered by a lack of understanding of the molecular mechanisms that underlie malignant transformation. De novo or acquired resistance to chemotherapy and radiation therapy remains an obstacle to cure. Ongoing discoveries of molecular and cellular mechanisms that explain the cancer process have led to increasingly specific antineoplastic therapies, generally referred to as **molecularly targeted therapies**. Their most prominent feature is a relative lack of normal tissue toxicity, such that the additional therapeutic benefit occurs with minimum additional toxicity. Many of the new biologic agent therapies, such as imatinib and rituximab, fall into this category (Table 494-1). Complementary and alternative remedies are increasingly being provided by parents to their children with cancer, with or without knowledge of the medical professionals entrusted with the child’s care (see Chapter 64). Many of these have not been evaluated by rigorous testing and most are ineffective; some are toxic or interfere with the metabolism of other drugs.

**DISCUSSING THE TREATMENT PLAN WITH THE PATIENT AND FAMILY**

The diagnostic and treatment plan must be carefully explained to parents and, if the child is old enough to understand, to the patient. An honest discussion of the facts is the best policy. Children should be given as much information as they can understand and would find useful or that information they express a desire or wish to know. Effects of treatment, such as the possible need to amputate a limb, loss of hair during chemotherapy, and possible temporary or permanent functional impairment must be anticipated and fully discussed. The possibility and probability of death from cancer should be covered in an age-appropriate manner. It usually is necessary to repeat explanations several times before distraught family members fully understand. Throughout treatment, parents, patients, siblings, and medical staff will need help in expressing feelings of anxiety, depression, guilt, and anger. The pediatrician, pediatric oncologist, and nurses should call on experienced professionals, including pediatric social workers, child
Table 494-1  Protein Tyrosine Kinase Inhibitors and Monoclonal Antibodies

<table>
<thead>
<tr>
<th>AGENT</th>
<th>TARGET</th>
<th>MALIGNANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>BCR-ABL</td>
<td>CML, Philadelphia chromosome-positive ALL</td>
</tr>
<tr>
<td></td>
<td>PDGFRα</td>
<td>Hypereosinophilic syndrome Systemic mastocytosis CMML Systemic mastocytosis Gastrointestinal stromal tumor</td>
</tr>
<tr>
<td>Dasatinib, Nilotinib</td>
<td>BCR-ABL</td>
<td>CML, Philadelphia chromosome-positive ALL</td>
</tr>
<tr>
<td>Gefitinib, Erlotinib, Cetuximab</td>
<td>EGFR</td>
<td>Non–small cell lung cancer</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ERBB2/HER-2</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGFR-1,-2</td>
<td>Non–small cell lung cancer Breast cancer Renal cell carcinoma Colorectal cancer Glioblastoma</td>
</tr>
</tbody>
</table>

ALL: Acute lymphoblastic leukemia; CML: chronic myelogenous leukemia; CMML: chronic myelomonocytic leukemia.

The most widely used modality in pediatric cancer therapy is chemotherapy (see Fig. 494-3). Therapy nearly always involves combinations of drugs, such as VAC (vincristine, dactinomycin [Actinomycin D], and cyclophosphamide) and CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin/Adriamycin], vincristine [Oncovin], and prednisone). Sequential single-drug therapy rarely results in complete responses, and partial responses usually are infrequent and transient and grow progressively shorter in duration with each drug used. Combination chemotherapy is the standard when combinations of drugs with different mechanisms of action and non-overlapping toxicities were first demonstrated to be effective in childhood leukemia. Most of the cytotoxic drugs for childhood cancer are selected from several classes of agents, including alkylating agents, antimetabolites, antibiotics, hormones, plant alkaloids, and topoisomerase inhibitors (Table 494-2). The increased metabolic and cell-cycle activity of malignant cells makes them more susceptible to the cytotoxic effects of these types of agents (Fig. 494-5).

Because most antineoplastic agents are cell-cycle dependent, their adverse effects usually are related to the proliferation kinetics of individual cell populations. Most susceptible are tissues or organs with high rates of cell turnover: bone marrow, oral and intestinal mucosa, epidermis, liver, and spermatogonia. The most common acute adverse

Table 494-2  Common Chemotherapeutic Agents Used in Children

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION OR CLASSIFICATION</th>
<th>INDICATION(S)</th>
<th>ADVERSE REACTIONS (PARTIAL LIST)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Folic acid antagonist; inhibits dihydrofolate reductase</td>
<td>ALL, non-Hodgkin lymphoma, osteosarcoma, Hodgkin lymphoma, medulloblastoma</td>
<td>Myelosuppression, mucositis, stomatitis, dermatitis, hepatitis With long-term administration; osteopenia and bone fractures With high-dose administration; renal and CNS toxicity With intrathecal administration; arachnoiditis, leukoencephalopathy, leukomyelopathy</td>
<td>Systemic administration may be PO, IM, or IV; also may be administered intrathecally Plasma methotrexate levels must be monitored with high-dose therapy and when low doses are administered to patients with renal dysfunction, and leucovorin rescue applied accordingly Allopurinol inhibits metabolism</td>
</tr>
<tr>
<td>6-Mercaptopurine (Purinethol)</td>
<td>Purine analog; inhibits purine synthesis</td>
<td>ALL</td>
<td>Myelosuppression, hepatic necrosis, mucositis; allopurinol increases toxicity</td>
<td></td>
</tr>
<tr>
<td>Cytarabine (cytosine arabinoside; Ara-C)</td>
<td>Pyrimidine analog; inhibits DNA polymerase</td>
<td>ALL, AML, non-Hodgkin lymphoma, Hodgkin lymphoma</td>
<td>Nausea, vomiting, myelosuppression, conjunctivitis, mucositis, CNS dysfunction With intrathecal administration; arachnoiditis, leukoencephalopathy, leukomyelopathy</td>
<td>Systemic administration may be PO, IM, or IV; may also be administered intrathecally</td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan)</td>
<td>Alkylates guanine; inhibits DNA synthesis</td>
<td>ALL, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, Ewing sarcoma, Wilms tumor, neuroblastoma</td>
<td>Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, bladder cancer, anaphylaxis</td>
<td>Requires hepatic activation and thus is less effective in presence of liver dysfunction Mesna prevents hemorrhagic cystitis</td>
</tr>
<tr>
<td>Ifosfamide (Ifex)</td>
<td>Alkylates guanine; inhibits DNA synthesis</td>
<td>Non-Hodgkin lymphoma, Wilms tumor, soft tissue sarcoma</td>
<td>Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, CNS dysfunction, cardiac toxicity, anaphylaxis</td>
<td>Mesna prevents hemorrhagic cystitis</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION OR CLASSIFICATION</th>
<th>INDICATION(S)</th>
<th>ADVERSE REACTIONS (PARTIAL LIST)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin (Adriamycin), daunorubicin (Cerubidine), and idarubicin (Idamycin)</td>
<td>Binds to DNA, intercalation</td>
<td>ALL, AML, osteosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma</td>
<td>Nausea, vomiting, cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia</td>
<td>Dexrazoxane reduces risk of cardiotoxicity</td>
</tr>
<tr>
<td>Dactinomycin</td>
<td>Binds to DNA, inhibits transcription</td>
<td>Wilm's tumor, rhabdomyosarcoma, Ewing sarcoma</td>
<td>Nausea, vomiting, tissue necrosis on extravasation, myelosuppression, radiosensitizer, mucosal ulceration</td>
<td></td>
</tr>
<tr>
<td>Bleomycin (Blenoxane)</td>
<td>Binds to DNA, cleaves DNA strands</td>
<td>Hodgkin disease, non-Hodgkin lymphoma, germ cell tumors</td>
<td>Nausea, vomiting, pneumonitis, stomatitis, Raynaud phenomenon, pulmonary fibrosis, dermatitis</td>
<td></td>
</tr>
<tr>
<td>Vincristine (Oncovin)</td>
<td>Inhibits microtubule formation</td>
<td>ALL, non-Hodgkin lymphoma, germ cell tumors</td>
<td>Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression</td>
<td>IV administration only; must not be allowed to extravasate</td>
</tr>
<tr>
<td>Vinblastine (Velban)</td>
<td>Inhibits microtubule formation</td>
<td>Hodgkin lymphoma, non-Hodgkin lymphoma, Langerhans cell histiocytosis, CNS tumors</td>
<td>Local cellulitis, leukopenia</td>
<td>IV administration only; must not be allowed to extravasate</td>
</tr>
<tr>
<td>L-Asparaginase</td>
<td>Depletion of L-asparagine</td>
<td>ALL; AML, when used in combination with cytarabine</td>
<td>Allergic reaction pancreatitis, hyperglycemia, platelet dysfunction and coagulopathy, encephalopathy</td>
<td>PEG-asparaginase now preferred to L-asparaginase</td>
</tr>
<tr>
<td>Pegaspargase (Oncaspar)</td>
<td>Polyethylene glycol conjugate of L-asparagine</td>
<td>ALL</td>
<td>Indicated for prolonged asparagine depletion and for patients with allergy to L-asparaginase</td>
<td></td>
</tr>
<tr>
<td>Prednisone and dexamethasone (Decadron)</td>
<td>Lymphatic cell lysis</td>
<td>ALL; Hodgkin lymphoma, non-Hodgkin lymphoma</td>
<td>Cushing syndrome, cataracts, diabetes, hypertension, myopathy, osteoporosis, avascular necrosis, infection, peptic ulceration, psychosis</td>
<td></td>
</tr>
<tr>
<td>Carmustine (BiCNU)</td>
<td>Carbamylation of DNA; inhibits DNA synthesis</td>
<td>CNS tumors, non-Hodgkin lymphoma, Hodgkin lymphoma</td>
<td>Nausea, vomiting, delayed myelosuppression (4-6 wk); pulmonary fibrosis, carcinogenic stomatitis</td>
<td>Phenobarbital increases metabolism, decreases activity</td>
</tr>
<tr>
<td>Carboplatin and cisplatin (Platinol)</td>
<td>Inhibits DNA synthesis</td>
<td>Osteosarcoma, neuroblastoma, CNS tumors, germ cell tumors</td>
<td>Nausea, vomiting, renal dysfunction, myelosuppression, ototoxicity, tetany, neurotoxicity, hemolytic-uremic syndrome, anaphylaxis</td>
<td>Aminoglycosides may increase nephrotoxicity</td>
</tr>
<tr>
<td>Etoposide (VePesid)</td>
<td>Topoisomerase inhibitor</td>
<td>ALL, non-Hodgkin lymphoma, germ cell tumor, Ewing sarcoma</td>
<td>Nausea, vomiting, myelosuppression, secondary leukemia</td>
<td></td>
</tr>
<tr>
<td>Tretinoin (all trans-retinoic acid); and isotretinoin (cis-retinoic acid; Accutane)</td>
<td>Enhances normal differentiation</td>
<td>Acute promyelocytic leukemia; neuroblastoma</td>
<td>Dry mouth, hair loss, pseudotumor cerebri, premature epiphyseal closure, birth defects</td>
<td></td>
</tr>
</tbody>
</table>

ADH, antidiuretic hormone; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CNS, central nervous system; PEG, polyethylene glycol.

effects are myelosuppression (with neutropenia and thrombocytopenia being the most problematic), immunosuppression, nausea and vomiting, hepatic dysfunction, upper and lower gastrointestinal mucositis, dermatitis, and alopecia. Fortunately, the tissues affected also recover relatively quickly, so that the acute adverse effects are nearly always reversible. Life-threatening effects of many chemotherapy agents include severe neutropenia with infection, fungemia or fungal pneumonia as a result of immunosuppression, and septicemia, not infrequently linked to indwelling intravascular devices (Table 494-3; see Chapters 178 and 179). Cardiomyopathy caused by anthracyclines (e.g., doxorubicin and daunorubicin) and renal failure from platinum-containing agents also may be life-threatening or disabling.
Figure 494-5 Site of action of the commonly used anticancer drugs. CMP, Cytidine monophosphate; dCMP, deoxycytidine monophosphate; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FH₂, dihydrofolate; FH₄, tetrahydrofolate. (Redrawn from Adamson PC, Balis FM, Blaney SM: General principles of chemotherapy. In Pizzo PA, Poplack DG, editors: Principles and practice of pediatric oncology, ed 6, Philadelphia, 2011, Lippincott Williams & Wilkins, p. 283.)

Table 494-3 Infectious Complications of Malignancy

<table>
<thead>
<tr>
<th>PREDISPOSING FACTOR</th>
<th>ETIOLOGY</th>
<th>SITE OF INFECTION</th>
<th>INFECTIOUS AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Chemotherapy, bone marrow infiltration</td>
<td>Sepsis, shock, pneumonia, soft tissue, proctitis, mucositis</td>
<td>Streptococcus viridans, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Candida, Aspergillus, anaerobic oral and rectal bacteria</td>
</tr>
<tr>
<td>Immunosuppression, lymphopenia, lymphocyte-monocyte dysfunction</td>
<td>Chemotherapy, corticosteroid</td>
<td>Pneumonia, meningitis, disseminated viral infection</td>
<td>Pneumocystis jiroveci, Cryptococcus neoformans, Mycobacterium, Nocardia, Listeria monocytogenes, Candida, Aspergillus, Strongyloides, Toxoplasma, varicella-zoster virus, cytomegalovirus, herpes simplex</td>
</tr>
<tr>
<td>Indwelling central venous catheter</td>
<td>Nutrition, administration of chemotherapy</td>
<td>Line sepsis, tract of tunnel, exit site</td>
<td>S. epidermidis, S. aureus, Candida albicans, P. aeruginosa, Aspergillus, Corynebacterium, Streptococcus faecalis, Mycobacterium fortuitum, Propionibacterium acnes</td>
</tr>
</tbody>
</table>


Least susceptible to chemotherapy and radiation therapy are cells that do not replicate or that replicate slowly, such as neurons, muscle cells, connective tissue, and bone. However, children are not exempt from toxicities of these tissues, probably because they are still undergoing proliferation albeit at a slower pace than other tissues, during growth and growth spurts.

Physically, children can endure the acute adverse effects of chemotherapy better than adults can in many ways. The maximum tolerated dosage in children, when expressed on the basis of body surface area or body weight, commonly is greater than that in adults. A comparison of anticancer drugs tested in phase 1 trials in both adult and pediatric patients showed that the maximum tolerated dosage in children was greater than that in adults for 70% of the agents, equal to that in adults for 15% of the agents, and less than the adult dose for only 15% of the agents. For all the drugs that were compared, the mean pediatric maximum tolerated dosage was greater than the adult mean.

Tumor-directed therapies are evolving in the field of pediatric oncology. Tumor antigen–specific monoclonal antibodies have been incorporated into the standard therapy of neuroblastoma (anti–ganglioside GD₃). The antiangiogenic agent bevacizumab (monoclonal antibody against vascular endothelial growth factor A) shows promise in the treatment of CNS tumors, especially low-grade gliomas.

**Surgery**

Superb pediatric surgical and anesthesia services are indispensable for children with cancer. The pediatric surgeon’s role varies, depending on the type of tumor. For solid tumors, complete resection with
documented evidence of negative margins often is required for cure or long-term control. Considerable prolongation of life nearly always depends on whether the tumor is resectable and on the actual extent of resection.

With the exception of brainstem tumors and retinoblastoma, all solid tumors in children require a tissue diagnosis; therefore, biopsy of the suspected neoplasm is paramount. Staging with sentinel node biopsies has become the standard of care for several pediatric malignancies. Surgical expertise is essential for implantation of vascular access devices and removal and replacement of such devices when infection or thrombosis supervenes (see Chapter 179).

Increasingly, minimally invasive endoscopic surgical techniques are being used when indicated and, if the patient’s condition permits, for biopsy and resection of tumor, direct ascertainment of residual disease and assessment of response, lysis of adhesions, and splenectomy.

**Radiation Therapy**

Radiation therapy is used sparingly in children, who are more susceptible than are adults to the adverse delayed effects of ionizing radiation. A major advance in pediatric radiation therapy is the application of conformal irradiation to children with cancer. This technique, most commonly applied as intensity-modulated radiation therapy, spares normal tissue by conforming the radiation volume to the shape of the tumor, thereby enabling delivery of higher doses to the tumor with lower exposure of normal tissue adjacent to the tumor or in the path of the radiation beam. Another example is proton-beam radiotherapy, which has just begun to be more widely available for children with cancer. With more focused beams and better sedation and immobilization techniques, radiation therapy is becoming more commonly used in children. Acute adverse effects from radiation therapy are less severe than those from chemotherapy and depend on which part of the body is irradiated and the means of administration. Dermatitis is the most common general adverse effect, because skin is always in the treatment field. Nausea and diarrhea are common subacute adverse effects with abdominal radiation therapy. Mucositis nearly always occurs to some extent whenever oral or intestinal mucosa is in the treatment volume. Somnolence is common with cranial irradiation. Alopecia occurs where hair is in the radiation field.

Most radiation therapy schedules require treatment 5 days per week for 4–7 wk, depending on the dose needed to control the tumor and on the amount and nature of normal tissue in the field. Most adverse effects are not noted until the second half of the course of irradiation. Late effects can occur months to years after radiation therapy and usually are dose-limiting manifestations. The type of delayed toxicity also depends on the site of irradiation. Examples are impaired growth resulting from cranial or vertebral irradiation, endocrine dysfunction from midbrain irradiation, pulmonary or cardiac insufficiency from chest irradiation, strictures and adhesions from abdominal irradiation, and infertility from pelvic irradiation. Second malignancy can also develop in the radiation field, for example, breast cancer from chest irradiation and brain tumors from CNS irradiation.

**ACUTE TOXIC EFFECTS AND SUPPORTIVE CARE**

Adverse treatment effects that occur early in therapy can result in oncologic emergencies. These include metabolic disorders, bone marrow suppression, and compression by tumors on vital structures (Table 494-4). In tumor lysis syndrome (TLS), uric acid, phosphates, and potassium are released in the circulation in large quantities from death of tumor cells. Hyperuricemia can lead to impairment of renal function. The serum levels of uric acid, electrolytes, calcium, phosphorus, and creatinine should be measured and adequate hydration ensured. Allopurinol (a xanthine oxidase inhibitor) should be started to prevent further accumulation of uric acid. In patients with established TLS with high uric acid levels or those at high risk for TLS, rasburicase (an enzyme that degrades uric acid) should be given instead of allo- purinol. Symptomatic hyperkalemia and hyperphosphatemia with subsequent hypocalcemia can develop in the setting of inadequate renal function.

Virtually all chemotherapy regimens can produce myelosuppression, as can malignancies that invade and replace bone marrow. Anemia can be corrected by transfusions of packed erythrocytes, and thrombocytopenia can be corrected by platelet infusions. Patients receiving immunosuppressive therapy should receive irradiated blood products to prevent graft-versus-host disease and leukoreduced blood products to prevent transfusion-associated reactions and infections. Neutropenia (neutrophil counts <500/µL) poses a risk of life-threatening infection. Febrile neutropenic patients should be hospitalized and treated with empiric broad-spectrum intravenous antimicrobial therapy pending the results of appropriate cultures of blood, urine, or any obvious sites of infection (see Chapter 178). Treatment is continued until fever resolves and the neutrophil count rises. If fever persists for more than 3-5 days while the patient is receiving broad-spectrum antibiotics, the possibility of fungal infection must be considered. Fungal infections caused by Candida and Aspergillus are common in immunosuppressed patients. Opportunistic organisms such as Pneumocystis jiroveci can produce fatal pneumonia. Prophylactic treatment with trimethoprim-sulfamethoxazole is given when severe or prolonged immunosuppression is anticipated.

**Viruses** of low pathogenicity can produce serious disease in the setting of immunosuppression caused by malignancy or its treatment. Patients should not be given live virus vaccines. Children who are receiving chemotherapy and who are exposed to chickenpox should receive varicella-zoster immunoglobulin, or, if varicella-zoster immunoglobulin is not available, oral acyclovir should be considered. If clinical disease develops, the child should be hospitalized and treated with intravenous acyclovir.

Adequate pain management is critical. The World Health Organization (WHO) guidelines are particularly useful in the management of pain associated with cancer and cancer therapy (see Chapter 62).

Depending on the type of cancer therapy, patients can lose more than 10% of body weight. Patients sometimes reduce their food intake because of temporary, treatment-associated nausea, stomatitis, and vomiting. Appetite loss is not a cause for alarm. Malnutrition is a particular risk in patients receiving radiation therapy involving the abdomen or the head and neck, intensive chemotherapy, or total-body irradiation and high-dose chemotherapy before marrow transplantation. If oral supplementation proves inadequate, such patients can require enteral tube feedings or parenteral hyperalimentation.

**LATE ADVERSE EFFECTS**

Injury to tissues with low repair potential often results in long-lasting or permanent deficit. These effects can be either from the tumor or its treatment. For example, a brain or spinal tumor can leave the child with a permanent paresis or autonomic dysfunction, anthracycline-induced cardiomyopathy usually produces refractory cardiac dysfunction, and the leukoencephalopathy caused by intrathecal methotrexate and by CNS radiation therapy often is only partially reversible. The potential types of late adverse effects depend on the child’s age at the time of treatment, the location(s) of the cancer, and the therapy administered. A good resource for the pediatrician, patient, and family who have to anticipate the possibilities is available at http://www.survivorshipguidelines.org.

Late adverse effects of therapy can cause substantial morbidity (Table 494-5). Successful surgical resection can result in loss of important functional structures. Irradiation can produce irreversible organ damage, with symptoms and functional limitations depending on the organ involved and the severity of the damage. Many problems related to radiation therapy do not become obvious until the patient is fully grown, such as asymmetry between irradiated and nonirradiated areas or extremities. Irradiation of fields that include endocrine organs can cause hypothyroidism, pituitary dysfunction, or infertility. In sufficient
Table 494-4  Oncologic Emergencies

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>MANIFESTATIONS</th>
<th>ETIOLOGY</th>
<th>MALIGNANCY</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>METABOLIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Uric acid nephropathy</td>
<td>Tumor lysis syndrome</td>
<td>Lymphoma, leukemia</td>
<td>Allopurinol, alkalinize urine; hydration and diuresis, rasburicase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kayexalate, sodium bicarbonate, glucose, and insulin; check for pseudohyperuricemia from leukemic cell lysis in test tube Hydroxymethionine to bind phosphate Restrict free water for SIADH; replace sodium if depleted Hydration and furosemide diuresis; corticosteroids; calcitonin, bisphosphonates</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Arrhythmias, cardiac arrest</td>
<td>Tumor lysis syndrome</td>
<td>Lymphoma, leukemia</td>
<td></td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Hypocalcemic tetany; metastatic calcification, photophobia, pruritus syndrome</td>
<td>Tumor lysis syndrome</td>
<td>Lymphoma, leukemia</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Seizure, lethargy (may also be asymptomatic)</td>
<td>SIADH; fluid, sodium losses in vomiting</td>
<td>Leukemia, CNS tumor</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Anorexia, nausea, polyuria, pancreatitis, gastric ulcers; prolonged PR, shortened QT interval</td>
<td>Bone resorption; ectopic parathormone, vitamin D, or prostaglandins</td>
<td>Metastasis to bone, rhabdomyosarcoma, leukemia</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>HEMATOLOGIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Pallor, weakness, heart failure</td>
<td>Bone marrow suppression or infiltration; blood loss</td>
<td>Any with chemotherapy</td>
<td>Packed red blood cell transfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Platelet transfusion</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Petechiae, hemorrhage</td>
<td>Bone marrow suppression or infiltration</td>
<td>Any with chemotherapy</td>
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<td></td>
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<tr>
<td>Disseminated intravascular coagulation Neutropenia</td>
<td>Shock, hemorrhage</td>
<td>Sepsis, hypotension, tumor factors</td>
<td>Promyelocytic leukemia, others</td>
<td>Fresh-frozen plasma; platelets, cryoprecipitate, treat underlying disorder If febrile, administer broad-spectrum antibiotics, and filgrastim (G-CSF) if appropriate</td>
</tr>
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<td></td>
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</tr>
<tr>
<td>Hyperleukocytosis (&gt;100,000/mm³)</td>
<td>Hemorrhage, thrombosis; pulmonary infiltrates, hypoxia; tumor lysis syndrome</td>
<td>Bone marrow suppression or infiltration</td>
<td>Any with chemotherapy</td>
<td></td>
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</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>Dermatitis, diarrhea, hepatitis</td>
<td>Immunosuppression and nonirradiated blood products; bone marrow transplantation</td>
<td>Any with immunosuppression</td>
<td>Corticosteroids; cyclosporine; tacrolimus; antithymocyte globulin</td>
</tr>
<tr>
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<tr>
<td>SPACE-OCCUPYING LESIONS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Spinal cord compression</td>
<td>Back pain ± radicular Cord above T10: symmetric weakness, increased deep tendon reflex; sensory level present; toes up Conus medullaris (T10-L2): symmetric weakness, increased knee reflexes; decreased ankle reflexes; saddle sensory loss; toes up or down Cauda equina (below L2): asymmetric weakness; loss of deep tendon reflex and sensory deficit; toes down</td>
<td>Metastasis to vertebra and extramedullary space</td>
<td>Neuroblastoma; medulloblastoma</td>
<td>MRI or myelography for diagnosis; corticosteroids; radiotherapy; laminectomy; chemotherapy</td>
</tr>
<tr>
<td>Increased intracranial pressure</td>
<td>Confusion, coma, emesis, headache, hypertension, bradycardia, seizures, papilledema, hydrocephalus; cranial nerves III and VI palsies</td>
<td>Primary or metastatic brain tumor</td>
<td>Neuroblastoma, astrocytoma, glioma</td>
<td>CT or MRI for diagnosis; corticosteroids; phenytoin; ventriculostomy tube; radiotherapy; chemotherapy</td>
</tr>
<tr>
<td>Superior vena cava syndrome</td>
<td>Distended neck veins plethora, edema of head and neck, cyanosis, proptosis, Horner syndrome</td>
<td>Superior mediastinal mass</td>
<td>Lymphoma</td>
<td>Chemotherapy; radiotherapy</td>
</tr>
<tr>
<td>Tracheal compression</td>
<td>Respiratory distress</td>
<td>Mediastinal mass compressing trachea</td>
<td>Lymphoma</td>
<td>Radiation, corticosteroids</td>
</tr>
</tbody>
</table>

CNS, Central nervous system; G-CSF, granulocyte colony-stimulating factor; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

### Table 494-5  
Late Effects and High-Risk Features of Childhood Cancer and Its Treatment

<table>
<thead>
<tr>
<th>LATE EFFECTS</th>
<th>EXPOSURE</th>
<th>SELECTED HIGH-RISK FACTORS</th>
<th>AT-RISK DIAGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEUROCOGNITIVE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurocognitive deficits</td>
<td></td>
<td></td>
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<tr>
<td>Functional deficits in:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Executive function</td>
<td></td>
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<td></td>
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<tr>
<td>- Sustained attention</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Processing speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Visual-motor integration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Learning deficits</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diminished IQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy:</td>
<td>Age &lt;3 yr at time of treatment</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td></td>
<td>• Methotrexate</td>
<td>Female sex</td>
<td>Brain tumor</td>
</tr>
<tr>
<td></td>
<td>Radiation affecting brain:</td>
<td>Supratentorial tumor</td>
<td>Sarcoma (head and neck or osteosarcoma)</td>
</tr>
<tr>
<td></td>
<td>• Cranial</td>
<td>Premorbid or family history of learning or attention problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ear/infratemporal</td>
<td>Radiation doses &gt;24 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Total-body irradiation (TBI)</td>
<td>Whole-brain irradiation</td>
<td></td>
</tr>
<tr>
<td><strong>NEUROSENSORY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss, sensorineural</td>
<td>Chemotherapy:</td>
<td>Higher cisplatin dose (360 mg/m²)</td>
<td>Brain tumor</td>
</tr>
<tr>
<td></td>
<td>• Cisplatin</td>
<td>Higher radiation dose impacting ear (&gt;30 Gy)</td>
<td>Germ cell tumor</td>
</tr>
<tr>
<td></td>
<td>• Carboplatin</td>
<td>Concurrent radiation and cisplatin</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td></td>
<td>Radiation affecting hearing:</td>
<td>Radiation dose to HPA &gt;18 Gy</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td></td>
<td>• Cranial</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Infratemporal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nasopharyngeal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss, conductive</td>
<td>Radiation affecting hearing:</td>
<td>Higher radiation dose affecting ear (&gt;30 Gy)</td>
<td>Brain tumor</td>
</tr>
<tr>
<td>Tympanosclerosis</td>
<td>• Cranial</td>
<td></td>
<td>Sarcoma (head and neck)</td>
</tr>
<tr>
<td>Otosclerosis</td>
<td>• Infratemporal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eustachian tube dysfunction</td>
<td>• Nasopharyngeal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual impairment</td>
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<td>Higher radiation dose impacting eye (≥15 Gy for cataracts; &gt;45 Gy for retinopathy and visual impairment)</td>
<td>Brain tumor</td>
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<tr>
<td>Cataracts</td>
<td>• Busulfan</td>
<td></td>
<td>Acute lymphoblastic leukemia</td>
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<td></td>
<td>• Glucocorticoids</td>
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<td>Retinoblastoma</td>
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<td></td>
<td>Radiation affecting eye:</td>
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<td>Rhabdomyosarcoma (orbital)</td>
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<td>• Cranial</td>
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<td>• Orbital/eye</td>
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<tr>
<td>Lacrimal duct atrophy</td>
<td>Higher cisplatin dose (≥300 mg/m²)</td>
<td>Acute lymphoblastic leukemia</td>
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<td>Xerophthalmia</td>
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<td>Brain tumor</td>
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<td>Glaucma</td>
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<td></td>
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<tr>
<td></td>
<td>Chemotherapy:</td>
<td></td>
<td>Sarcoma</td>
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<tr>
<td></td>
<td>• Vincristine</td>
<td></td>
<td>Neuroblastoma</td>
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<td>• Vinblastine</td>
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<td>Wilms tumor</td>
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<td>Carcinoma</td>
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<td><strong>NEUROMOTOR</strong></td>
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<tr>
<td>Peripheral neuropathy, motor</td>
<td>Chemotherapy:</td>
<td></td>
<td>Acute lymphoblastic leukemia</td>
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<tr>
<td></td>
<td>• Vincristine</td>
<td></td>
<td>Hodgkin lymphoma</td>
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<td>• Vinblastine</td>
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<td>Non-Hodgkin lymphoma</td>
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<td>Sarcoma</td>
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<td>Brain tumor</td>
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<td>Neuroblastoma</td>
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<td></td>
<td></td>
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<td>Wilms tumor</td>
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<td><strong>ENDOCRINE</strong></td>
<td></td>
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</tr>
<tr>
<td>GH deficiency</td>
<td>Radiation affecting HPA:</td>
<td>Female sex</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td></td>
<td>• Cranial</td>
<td>Radiation dose to HPA &gt;18 Gy</td>
<td>Sarcoma (facial)</td>
</tr>
<tr>
<td></td>
<td>• Orbital/eye</td>
<td></td>
<td>Carcinoma (nasopharyngeal)</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td></td>
<td></td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female sex</td>
<td>Brain tumor</td>
</tr>
<tr>
<td>Obesity</td>
<td>Ear/infratemporal</td>
<td>Younger age (&lt;4 yr)</td>
<td>Sarcoma (facial)</td>
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<td></td>
<td>Nasopharyngeal</td>
<td>Radiation dose to HPA &gt;18 Gy</td>
<td>Carcinoma (nasopharyngeal)</td>
</tr>
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<td></td>
<td>TBI</td>
<td></td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Hypothyroidism, central</td>
<td>Neck, mantle irradiation</td>
<td>Radiation dose to thyroid &gt;20 Gy</td>
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### Table 494-5  Late Effects and High-Risk Features of Childhood Cancer and Its Treatment—cont’d

<table>
<thead>
<tr>
<th>LATE EFFECTS</th>
<th>EXPOSURE</th>
<th>SELECTED HIGH-RISK FACTORS</th>
<th>AT-RISK DIAGNOSTIC GROUPS</th>
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<tr>
<td><strong>REPRODUCTIVE</strong></td>
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<tr>
<td>Gonadal dysfunction</td>
<td>Chemotherapy, alkylating:</td>
<td>Higher alkylating agent dose</td>
<td>Acute lymphoblastic leukemia, high risk</td>
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<tr>
<td>Delayed or arrested puberty</td>
<td>• Busulfan</td>
<td>Alkylating agent conditioning for HSCT</td>
<td>Brain tumor</td>
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<td>Premature menopause</td>
<td>• Carmustine (BCNU)</td>
<td>Radiation dose ≥15 Gy in prepubertal girls</td>
<td>Hodgkin lymphoma, advanced or unfavorable</td>
</tr>
<tr>
<td>Germ cell dysfunction or</td>
<td>• Chlorambucil</td>
<td>Radiation dose ≥10 Gy in pubertal girls</td>
<td>Non-Hodgkin lymphoma, advanced or</td>
</tr>
<tr>
<td>failure</td>
<td>• Cyclophosphamide</td>
<td>For germ cell failure in boys, any pelvic irradiation</td>
<td>unfavorable Sarcoma</td>
</tr>
<tr>
<td>Infertility</td>
<td>• Ifosfamide</td>
<td>For androgen insufficiency, gonadal irradiation, ≥20-30 Gy in</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td></td>
<td>• Lomustine (CCNU)</td>
<td>boys</td>
<td>Wilms tumor, advanced</td>
</tr>
<tr>
<td></td>
<td>• Mechlothamine</td>
<td></td>
<td>Autologous or allogeneic HSCT</td>
</tr>
<tr>
<td></td>
<td>• Procarbazine</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Radiation affecting reproductive system:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Whole abdomen (girls)</td>
<td></td>
<td></td>
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<td></td>
<td>• Pelvic</td>
<td></td>
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<td></td>
<td>• Lumbar/sacral spine (girls)</td>
<td></td>
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<td></td>
<td>• Testicular (boys)</td>
<td></td>
<td></td>
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<td></td>
<td>• TBI</td>
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<td><strong>CARDIAC</strong></td>
<td></td>
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</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Chemotherapy:</td>
<td>Female sex</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>• Daunorubicin</td>
<td>Age &lt;5 yr at time of treatment</td>
<td>Leukemia</td>
</tr>
<tr>
<td></td>
<td>• Doxorubicin</td>
<td>Higher doses of chemotherapy (≥300 mg/m²)</td>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td></td>
<td>• Idarubicin</td>
<td>Higher doses of cardiac radiation (≥30 Gy)</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Radiation affecting heart:</td>
<td>Combined-modality therapy with cardiotoxic chemotherapy and</td>
<td>Wilms tumor</td>
</tr>
<tr>
<td></td>
<td>• Chest</td>
<td>irradiation</td>
<td>Neuroblastoma</td>
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<td></td>
<td>• Mante</td>
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<tr>
<td></td>
<td>• Mediastinum</td>
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<td></td>
<td>• Axilla</td>
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<td></td>
<td>• Spine</td>
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<td></td>
<td>• Upper abdomen</td>
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<tr>
<td><strong>PULMONARY</strong></td>
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<td></td>
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<td>Pulmonary fibrosis</td>
<td>Chemotherapy:</td>
<td>Higher doses of chemotherapy</td>
<td>Brain tumor</td>
</tr>
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<td>Interstitial pneumonitis</td>
<td>• Bleomycin</td>
<td>Combined modality therapy with pulmonary toxic chemotherapy</td>
<td>Germ cell tumor</td>
</tr>
<tr>
<td>Restrictive lung disease</td>
<td>• Busulfan</td>
<td>and irradiation</td>
<td>Hodgkin lymphoma (chest wall or</td>
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<tr>
<td>Obstructive lung disease</td>
<td>• Carmustine (BCNU)</td>
<td></td>
<td>intrathoracic)</td>
</tr>
<tr>
<td></td>
<td>• Lomustine (CCNU)</td>
<td></td>
<td>Autologous or allogeneic HSCT</td>
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<tr>
<td></td>
<td>Radiation impacting lungs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mantle</td>
<td></td>
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<tr>
<td></td>
<td>• Mediastinum</td>
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<tr>
<td></td>
<td>• Whole lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• TBI</td>
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<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
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<tr>
<td>Chronic enterocolitis</td>
<td>Radiation affecting gastrointestinal tract:</td>
<td>Higher radiation dose to bowel (≥45 Gy)</td>
<td>Sarcoma (retroperitoneal or pelvic</td>
</tr>
<tr>
<td>Strictures</td>
<td>(≥30 Gy)</td>
<td>Combined modality therapy with abdominal irradiation and</td>
<td>primary)</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>Abdominal surgery</td>
<td>radiomimetic chemotherapy (dactinomycin or anthracyclines)</td>
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<tr>
<td></td>
<td></td>
<td>Combined modality therapy with abdominal surgery and</td>
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<td></td>
<td></td>
<td>irradiation</td>
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<tr>
<td><strong>HEPATIC</strong></td>
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<tr>
<td>Hepatic fibrosis</td>
<td>Radiation affecting liver</td>
<td>Higher radiation dose or treatment volume (20-30 Gy to entire</td>
<td>Sarcoma</td>
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<tr>
<td>Cirrhosis</td>
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<td>liver or ≥40 Gy to at least one third of liver)</td>
<td>Neuroblastoma</td>
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<tr>
<td><strong>RENAL</strong></td>
<td></td>
<td></td>
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<td>Renal insufficiency</td>
<td>Chemotherapy:</td>
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<td>Hypertension</td>
<td>• Ifosfamide</td>
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<td>Glomerular injury</td>
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<td>Tubular injury</td>
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<td>Radiation affecting kidneys:</td>
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<td></td>
<td>• Whole abdomen</td>
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<td></td>
<td>• Upper abdominal fields</td>
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<td></td>
<td>• TBI</td>
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</tbody>
</table>

GH, Growth hormone; HPA, hypothalamic–pituitary–adrenal axis; HSCT, hematopoietic stem cell transplantation; TBI, total-body irradiation.

**Group 1. Low risk of late effects:**
- Surgery only
- Chemotherapy did not include alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- No radiation

**Group 2. Moderate risk:**
- Low or moderate dose alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- No radiation

**Group 3. High risk:**
- Any radiation
- High dose alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- Stem cell transplant

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**Communication points with primary care physician**

a. Cancer diagnosis and planned therapeutic approach, brief overview of chemotherapy, radiation therapy, and/or surgery
b. Cancer summary: cancer diagnosis, cancer therapy, surveillance recommendations, contact information
c. Periodic update with changes in surveillance recommendations and new information regarding potential late effects
d. Periodic update of survivor’s health for primary care physician’s record

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**Figure 494-6 Proposed risk-stratified shared care model for childhood cancer survivors.** Solid line denotes primary responsibility for risk-based care; risk stratification based upon determination of the long-term follow-up staff. CA, Cancer; DX, diagnosis; Onc, oncologist; PCP, primary care provider; RX, therapy. (Adapted from Oeffinger KC, McCabe MS. Models for delivering survivorship care, J Clin Oncol 24(32):5119, 2006; with permission from the American Society of Clinical Oncology. From Oeffinger KC, Nathan PC, Kremer LCM: Challenges after curative treatment for childhood cancer and long-term follow up of survivors, Pediatr Clin North Am 55:251–273, 2008.)

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doses, cranial irradiation can produce neurologic dysfunction and spinal irradiation can produce growth retardation.

Chemotherapy also carries the risk of long-lasting organ damage. Of particular concern are leukoencephalopathy after high-dose methotrexate therapy; infertility in male patients treated with alkylating agents (e.g., cyclophosphamide); myocardial damage caused by anthracyclines; pulmonary fibrosis caused by bleomycin; renal dysfunction caused by ifosfamide, nitrosourea, or platinum agents; and hearing loss from cisplatin. Development of these sequelae may be dose-related and usually is irreversible. Appropriate baseline and intermittent testing should be performed before these drugs are administered to ensure that there is no preexisting damage to the organs likely to be affected and to permit monitoring of the adverse effects of treatment-induced changes.

Perhaps the most serious late adverse effect is the occurrence of second cancers in patients successfully cured of a first malignancy. The risk appears to be cumulative, increasing by approximately 0.5% per year, resulting in approximately a 12% incidence at 25 yr after treatment. Patients who have been treated for childhood cancer should be examined annually, with particular attention to possible late adverse effects of therapy, including second malignancies (Fig. 494-6).

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**PALLIATIVE CARE**

At all stages of caring for children with cancer, principles of palliative care should be applied to relieve pain and suffering and to provide comfort (see Chapter 43). Pain is a serious cause of suffering among patients with cancer. It may be the result of organ obstruction or compression or bone metastasis, or it may be neuropathic. Pain should be managed in a stepwise manner, as recommended by the WHO, in accordance with the principles of selecting the appropriate analgesic, prescribing the appropriate dosage, administering the drug by the appropriate route, and choosing an appropriate dosing schedule to prevent persistent pain and to relieve breakthrough pain (see Chapter 62). In addition, the dosage should be titrated aggressively while attempts are made to prevent, anticipate, and manage side effects. Adjuvant drugs and sequential trials of analgesic drugs should be considered.

The goals in the care of dying patients are to avoid distress for the patient, family, and caregivers; to provide care consistent with the patient’s and family’s wishes; and to comply with and advocate for clinical, cultural, and ethical standards.

*Bibliography is available at Expert Consult.*
Chapter 494  •  Principles of Treatment  2436.e1

Bibliography
Chapter 495

The Leukemias

David G. Tubergen, Archie Bleyer, A. Kim Ritchey, and Erika Friehling

The leukemias are the most common malignant neoplasms in childhood, accounting for approximately 31% of all malignancies that occur in children younger than 15 yr of age. Each year leukemia is diagnosed in approximately 3,250 children younger than 15 yr of age in the United States, an annual incidence of 4.5 cases per 100,000 children. Acute lymphoblastic leukemia (ALL) accounts for approximately 77% of cases of childhood leukemia, acute myelogenous leukemia (AML) for approximately 11%, chronic myelogenous leukemia (CML) for 2-3%, and juvenile myelomonocytic leukemia (JMML) for 1-2%. The remaining cases consist of a variety of acute and chronic leukemias that do not fit classic definitions for ALL, AML, CML, or JMML.

The leukemias may be defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to an unregulated clonal proliferation of cells. The progeny of these cells have a growth advantage over normal cellular elements, because of their increased rate of proliferation and a decreased rate of spontaneous apoptosis. The result is a disruption of normal marrow function and, ultimately, marrow failure. The clinical features, laboratory findings, and responses to therapy vary depending on the type of leukemia.

495.1 Acute Lymphoblastic Leukemia

Erika Friehling, A. Kim Ritchey, David G. Tubergen, and Archie Bleyer

Childhood ALL was the first disseminated cancer shown to be curable. It actually is a heterogeneous group of malignancies with a number of distinctive genetic abnormalities that result in varying clinical behaviors and responses to therapy.

EPIDEMIOLOGY

ALL is diagnosed in approximately 2,400 children younger than 15 yr of age in the United States each year. ALL has a striking peak incidence at 2-3 yr of age and occurs more in boys than in girls at all ages. This peak age incidence was apparent decades ago in white populations in advanced socioeconomic countries, but it has since been confirmed in the black population of the United States as well. The disease is more common in children with certain chromosomal abnormalities, such as Down syndrome, Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia. Among identical twins, the risk to the second twin if 1 twin develops leukemia is greater than that in the general population. The risk is >70% if ALL is diagnosed in the first twin during the 1st yr of life and the twins shared the same (monochorionic) placenta. If the first twin develops ALL by 5-7 yr of age, the risk to the second twin is at least twice that of the general population, regardless of zygosity.

ETIOLOGY

In virtually all cases, the etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia (Table 495-1). Most cases of ALL are thought to be caused by postconception somatic mutations in lymphoid cells. However, the identification of the leukemia-specific fusion-gene sequences in archived neonatal blood spots of some children who develop ALL at a later date indicates the importance of in utero events in the initiation of the malignant process in some cases. The long lag period before the onset of the disease in some children, reported to be as long as 14 yr, supports the concept that additional genetic modifications are required for disease expression. Moreover, those same mutations have been found in neonatal blood spots of children who never go on to develop leukemia.

Exposure to medical diagnostic radiation both in utero and in childhood is associated with an increased incidence of ALL. In addition, published descriptions and investigations of geographic clusters of cases have raised concern that environmental factors can increase the incidence of ALL. Thus far, no such factors other than radiation have been identified in the United States. In certain developing countries, there is an association between B-cell ALL (B-ALL) and Epstein-Barr viral infections.

CELLULAR CLASSIFICATION

The classification of ALL depends on characterizing the malignant cells in the bone marrow to determine the morphology, phenotype as measured by cell membrane markers, and cytogenetic and molecular genetic features. Morphology is usually adequate alone to establish a diagnosis, but the other studies are essential for disease classification, which can have a major influence on the prognosis and the choice of appropriate therapy. The current system used is the World Health Organization (WHO) classification of leukemias. Phenotypically, surface markers show that approximately 85% of cases of ALL are classified as B lymphoblastic leukemia (previously termed precursor B-ALL or pre-B-ALL), approximately 15% are T-lymphoblastic leukemia, and approximately 1% are derived from mature B cells. The rare leukemia of mature B cells is termed Burkitt leukemia and is one of the most rapidly growing cancers in humans, requiring a different therapeutic approach than other subtypes of ALL. A small percentage of children with leukemia have a disease characterized by surface markers of both lymphoid and myeloid derivation.

Chromosomal abnormalities are used to subclassify ALL into prognostic groups (Table 495-2). Many genetic alterations, including inactivation of tumor-suppressor genes and mutations that activate the NOTCH1 or RAS pathways, have been discovered and might one day be incorporated into clinical practice (Fig. 495-1).

The polymerase chain reaction and fluorescence in situ hybridization techniques offer the ability to pinpoint molecular genetic abnormalities and can be used to detect small numbers of malignant cells at diagnosis as well as during follow-up (minimal residual disease [MRD], see below) and are of proven clinical utility. The development of DNA microanalysis makes it possible to analyze the expression of thousands of genes in the leukemic cell. This technique promises to further enhance the understanding of the fundamental biology and to provide clues to the therapeutic approach of ALL.

CLINICAL MANIFESTATIONS

The initial presentation of ALL usually is nonspecific and relatively brief. Anorexia, fatigue, malaise, and irritability often are present, as is...
Table 495-2 Common Chromosomal Abnormalities in Acute Lymphoblastic Leukemia of Childhood

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>CHROMOSOMAL ABNORMALITY</th>
<th>GENETIC ALTERATION</th>
<th>PROGNOSIS</th>
<th>INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-ALL</td>
<td>Trisomies 4, 10, and 17</td>
<td>—</td>
<td>Favorable</td>
<td>25%</td>
</tr>
<tr>
<td>B-ALL</td>
<td>t(12;21)</td>
<td>ETV6-RUNX1</td>
<td>Favorable</td>
<td>20-25%</td>
</tr>
<tr>
<td>B-ALL</td>
<td>t(1;19)</td>
<td>E2A-PBX</td>
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<td>5-6%</td>
</tr>
<tr>
<td>B-ALL</td>
<td>t(4;11)</td>
<td>MLL-AF4</td>
<td>Unfavorable</td>
<td>2%</td>
</tr>
<tr>
<td>B-ALL</td>
<td>t(9;22)</td>
<td>BCR-ABL</td>
<td>Unfavorable</td>
<td>3%</td>
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<tr>
<td>Mature B-cell leukemia (Burkitt)</td>
<td>t(8;14)</td>
<td>IGH-MYC</td>
<td>None</td>
<td>1-2%</td>
</tr>
<tr>
<td>B-ALL</td>
<td>Hyperdiploidy</td>
<td>—</td>
<td>Favorable</td>
<td>20-25%</td>
</tr>
<tr>
<td>B-ALL</td>
<td>Hypodiploidy</td>
<td>—</td>
<td>Unfavorable</td>
<td>1%</td>
</tr>
<tr>
<td>T-ALL</td>
<td>t(10;14)</td>
<td>TLX1/HOX11</td>
<td>Favorable</td>
<td>5-10%</td>
</tr>
<tr>
<td>Infant</td>
<td>11q23</td>
<td>MLL rearrangements</td>
<td>Unfavorable</td>
<td>2-10%</td>
</tr>
</tbody>
</table>

Figure 495-1 Estimated frequency of specific genotypes in childhood ALL. The genetic lesions that are exclusively seen in cases of T-cell ALL are indicated in gold and those commonly associated with B-cell ALL in blue. The darker gold or blue color indicates those subtypes generally associated with poor prognosis. (From Pui CH, Mullighan CG, Evans WE. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood 2012;119(13):1165–1174, 2012.)

an intermittent, low-grade fever. Bone or joint pain, particularly in the lower extremities, may be present. Less commonly, symptoms may be of several months’ duration, may be localized predominantly to the bones or joints, and can include joint swelling. Bone pain is severe and can wake the patient at night. As the disease progresses, signs and symptoms of bone marrow failure become more obvious with the occurrence of pallor, fatigue, exercise intolerance, bruising, or epistaxis, as well as fever, which may be caused by infection or the disease. Organ infiltration can cause lymphadenopathy, hepatosplenomegaly, testicular enlargement, or central nervous system (CNS) involvement (cranial neuropathies, headache, seizures). Respiratory distress may be due to severe anemia or mediastinal node compression of the airways.

On physical examination, findings of pallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage can reflect bone marrow failure (see Chapter 493). The proliferative nature of the disease may be manifested as lymphadenopathy, splenomegaly, or, less commonly, hepatomegaly. In patients with bone or joint pain, there may be exquisite tenderness over the bone or objective evidence of joint swelling and effusion. Nonetheless, with marrow involvement, deep bone pain may be present but tenderness will not be elicited. Rarely, patients show signs of increased intracranial pressure that indicate leukemic involvement of the CNS. These include papilledema (see Fig. 493-3), retinal hemorrhages, and cranial nerve palsies. Respiratory distress usually is related to anemia but can occur in patients with an obstructive airway problem (wheezing) as the result of a large anterior mediastinal mass (e.g., in the thymus or nodes). This problem is most typically seen in adolescent boys with T-cell ALL (T-ALL). T-ALL also usually has a higher leukocyte count.

B-lymphoblastic leukemia is the most common immunophenotype, with onset at 1-10 yr of age. The median leukocyte count at presentation is 33,000/µL, although 75% of patients have counts <20,000/µL; thrombocytopenia is seen in 75% of patients, and hepatosplenomegaly is seen in 30-40% of patients. In all types of leukemia, CNS symptoms are seen at presentation in 5% of patients (5-10% have blasts in the cerebrospinal fluid [CSF]). Testicular involvement is rarely evident at diagnosis, but prior studies indicate occult involvement in 25% of boys. There is no indication for testicular biopsy.

DIAGNOSIS

The diagnosis of ALL is strongly suggested by peripheral blood findings that indicate bone marrow failure. Anemia and thrombocytopenia are seen in most patients. Leukemic cells might not be reported in the peripheral blood in routine laboratory examinations. Many patients with ALL present with total leukocyte counts of <10,000/µL. In such cases, the leukemic cells often are reported initially to be atypical lymphocytes, and it is only on further evaluation that the cells are found to be part of a malignant clone. When the results of an analysis of peripheral blood suggest the possibility of leukemia, the bone marrow should be examined promptly to establish the diagnosis. It is important that all studies necessary to confirm a diagnosis and adequately classify the type of leukemia be performed, including bone marrow aspiration and biopsy, flow cytometry, cytogenetics, and molecular studies.

ALL is diagnosed by a bone marrow evaluation that demonstrates >25% of the bone marrow cells as a homogeneous population of lymphoblasts. Initial evaluation also includes CSF examination. If lymphoblasts are found and the CSF leukocyte count is elevated, overt CNS or meningeal leukemia is present. This finding reflects a worse stage and indicates the need for additional CNS and systemic therapies. The staging lumbar puncture may be performed in conjunction with the first dose of intrathecal chemotherapy, if the diagnosis of leukemia was previously established from bone marrow evaluation. An experienced proceduralist should perform the initial lumbar puncture, because a traumatic lumbar puncture is associated with an increased risk of CNS relapse.
DIFFERENTIAL DIAGNOSIS
The diagnosis of leukemia is readily made in the patient with typical signs and symptoms, anemia, thrombocytopenia, and elevated white blood count with blasts present on smear. Elevation of the lactate dehydrogenase is often a clue to the diagnosis of ALL. When only pancytopenia is present, aplastic anemia (congenital or acquired) and myelofibrosis should be considered. Failure of a single cell line, as seen in transient erythroidblastopenia of childhood, immune thrombocytopenia, and congenital or acquired neutropenia, is rarely the presenting feature of ALL. A high index of suspicion is required to differentiate ALL from infectious mononucleosis in patients with acute onset of fever and lymphadenopathy and from juvenile idiopathic arthritis in patients with fever, bone pain but often no tenderness, and joint swelling. These presentations also can require bone marrow examination.

ALL must be differentiated from AML and other malignant diseases that invade the bone marrow and can have clinical and laboratory findings similar to ALL, including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and retinoblastoma.

TREATMENT
The single most important prognostic factor in ALL is the treatment: without effective therapy, the disease is fatal. Considerable progress has been made in event-free survival for children with ALL since the 1970s through use of multiagent chemotherapeutic regimens, intensification of therapy, and selection of treatment based upon relapse risk (Fig. 495-2). Survival is also related to age (Fig. 495-3) and subtype (Fig. 495-4).

Risk-directed therapy has become the standard of current ALL treatment and takes into account age at diagnosis, initial white blood cell count, immunophenotypic and cytogenetic characteristics of blast populations, rapidity of early treatment response (i.e., how quickly the leukemic cells can be cleared from the marrow or peripheral blood),

![Figure 495-2 Kaplan-Meier analyses of event-free survival (A) and overall survival (B) in 2,628 children with newly diagnosed ALL. The patients participated in 15 consecutive studies conducted at St. Jude Children’s Research Hospital from 1962-2005. The 5 yr event-free and overall survival estimates (±SE) are shown, except for Study 15, for which preliminary results at 4 yr are provided. The results demonstrate steady improvement in clinical outcome over the past 4 decades. The difference in event-free and overall survival rates has narrowed in the more recent periods, suggesting that relapses or second cancers that occur after contemporary therapy are more refractory to treatment. (From Pui CH, Evans WE: Treatment of acute lymphoblastic leukaemia, N Engl J Med 354:166–178, 2006.)

![Figure 495-3 Kaplan-Meier estimates of event-free survival according to age at diagnosis of acute lymphoblastic leukemia. (From Pui CH, Robinson LL, Look AT: Acute lymphoblastic leukaemia, Lancet 371:1030–1042, 2008.)
Higher levels of MRD present at the end of induction suggest a poorer estimate of the burden of leukemic cells present in the marrow. Specialized flow cytometry. MRD can be quantitative and can provide translocations and other DNA markers contained in leukemic cells or MRD end of the induction phase. Patients in clinical remission can have responded more rapidly.

Approach, the event-free survival has improved from 30% to 70%. The backbone. Imatinib is an agent specifically designed to inhibit the cally changed by the addition of imatinib to an intensive chemotherapy of Philadelphia chromosome positive ALL with t(9;22) has dramati specific chromosomal abnormalities, such as t(4;11), have an even higher therapy. Infants with ALL, along with patients who present with spe 17), and rearrangements of the therapy, hyperdiploidy, trisomy of specific chromosomes (4, 10, and 17), and rearrangements, portend a poorer outcome. Other mutations, such as in the IKZF1 gene, have been shown to be associated with a poor prognosis and may become important in treatment algorithms in the future. More favorable characteristics include a rapid response to therapy, hyperdiploidy, trisomy of specific chromosomes (4, 10, and 17), and rearrangements of the ETV6-RUNXI (formerly TEL-AML1) genes.

The outcome for patients at higher risk can be improved by administration of more intensive therapy despite the greater toxicity of such therapy. Infants with ALL, along with patients who present with specific chromosomal abnormalities, such as t(4;11), have an even higher risk of relapse despite intensive therapy. However, the poor outcome of Philadelphia chromosome positive ALL with t(9;22) has dramatically changed by the addition of imatinib to an intensive chemotherapy backbone. Imatinib is an agent specifically designed to inhibit the BCR-ABL kinase resulting from the translocation. With this new approach, the event-free survival has improved from 30% to 70%. Clinical trials demonstrate that the prognosis for patients with a slower response to initial therapy may be improved by therapy that is more intensive than the therapy considered necessary for patients who respond more rapidly. Most children with ALL are treated in clinical trials conducted by national or international cooperative groups. Standard treatment involves chemotherapy for 2-3 yr and most achieve remission at the end of the induction phase. Patients in clinical remission can have MRD that can only be detected with specific molecular probes to translocations and other DNA markers contained in leukemic cells or specialized flow cytometry. MRD can be quantitative and can provide an estimate of the burden of leukemic cells present in the marrow. Higher levels of MRD present at the end of induction suggest a poorer prognosis and higher risk of subsequent relapse. MRD of >0.01% on the marrow on day 29 of induction is a significant risk factor for shorter event-free survival for all risk categories, when compared with patients with negative MRD. Therapy for ALL intensifies treatment in patients with evidence of MRD at the end of induction.

Initial therapy, termed remission induction, is designed to eradicate the leukemic cells from the bone marrow. During this phase, therapy is given for 4 wk and consists of vincristine weekly, a corticosteroid such as dexamethasone or prednisone, and usually a single dose of a long-acting, pegylated asparaginase preparation. Patients at higher risk also receive daunomycin at weekly intervals. With this approach, 98% of patients are in remission, as defined by <5% blasts in the marrow and a return of neutrophil and platelet counts to near-normal levels after 4-5 wk of treatment. Intrathecal chemotherapy is always given at the start of treatment and at least once more during induction.

The second phase of treatment, consolidation, focuses on intensive CNS therapy in combination with continued intensive systemic therapy in an effort to prevent later CNS relapses. Intrathecal chemotherapy is given repeatedly by lumbar puncture. The likelihood of later CNS relapse is thereby reduced to <5%, from historical incidence as high as 60%. A small percentage of patients with features that predict a high risk of CNS relapse may receive irradiation to the brain in later phases of therapy. This includes patients who, at the time of diagnosis, have lymphoblasts in the CSF and either an elevated CSF leukocyte count or physical signs of CNS leukemia, such as cranial nerve palsies. Subsequently, many regimens provide 14-28 wk of therapy, with the drugs and schedules used varying depending on the risk group of the patient. This period of treatment is often termed intensification and includes phases of aggressive treatment (delayed intensification) as well as relatively nontoxic phases of treatment (interim maintenance). Multiantigen chemotherapy, including such medications as cytarabine, methotrexate, asparaginase, and vincristine, is used during these phases to eradicate residual disease. Finally, patients enter the maintenance phase of therapy, which lasts for 2-3 yr, depending on the protocol used. Patients are given daily mercaptopurine and weekly oral methotrexate, usually with intermittent doses of vincristine and a corticosteroid. A small number of patients with particularly poor prognostic features, such as those with induction failure or extreme hypodiploidy, may undergo bone marrow transplantation during the first remission.
Adolescents and young adults with ALL have an inferior prognosis compared to children younger than 15 yr old. They often have adverse prognostic factors and require more intensive therapy. Patients in this age group have a superior outcome when treated with pediatric as opposed to adult treatment protocols (Fig. 495-5). Although the explanation for these findings may be multifactorial, it is important that these patients be treated with pediatric treatment protocols, ideally in a pediatric cancer center.

There are genetic polymorphisms of enzymes important in the metabolism of drugs used in ALL. Pharmacogenetic testing of the thiopurine S-methyltransferase (TPMT) gene, which encodes one of the metabolizing enzymes of mercaptopurine, can identify patients who are wild type (normal TPMT enzyme activity), heterozygous (slightly decreased TPMT enzyme activity), or homozygous (low or absent enzyme activity). Decreased TPMT enzyme activity results in a toxic metabolite of mercaptopurine and results in severe myelosuppression, requiring dose reductions of the chemotherapy (see Chapter 59). In the future, treatment also may be stratified by gene expression profiles of leukemic cells. In particular, gene expression arrays induced by exposure to a chemotherapeutic agent can predict which patients have drug-resistant ALL.

**Treatment of Relapse**

The major impediment to a successful outcome is relapse of the disease. Outcomes remain poor among those that relapse, with the most important prognostic indicators being time from diagnosis and the site of relapsed disease. In addition, other factors, such as immunophenotype (T-ALL worse than B-ALL) and age at initial diagnosis, have prognostic significance.

Relapse occurs in the bone marrow in 15-20% of patients with ALL and carries the most serious implications, especially if it occurs during or shortly after completion of therapy. Intensive chemotherapy with agents not previously used in the patient followed by allogeneic stem cell transplantation can result in long-term survival for some patients with bone marrow relapse (see Chapter 135).

The incidence of CNS relapse has decreased to <5% since introduction of preventive CNS therapy. CNS relapse may be discovered at the time of a routine lumbar puncture in the asymptomatic patient. Symptomatic patients with relapse in the CNS usually present with signs and symptoms of increased intracranial pressure and can present with isolated cranial nerve palsies. The diagnosis is confirmed by demonstrating the presence of leukemic cells in the CSF. The treatment includes intrathecal medication and cranial or craniospinal irradiation. Systemic chemotherapy also must be used, because these patients are at high risk for subsequent bone marrow relapse. Most patients with leukemic relapse confined to the CNS do well, especially those in whom the CNS relapse occurs longer than 18 mo after initiation of chemotherapy.

Testicular relapse occurs in less than 2% of boys with ALL, usually after completion of therapy. Such relapse occurs as painless swelling of 1 or both testes. The diagnosis is confirmed by biopsy of the affected testis. Treatment includes systemic chemotherapy and possibly local irradiation. A high proportion of boys with a testicular relapse can be successfully retreated, and the survival rate of these patients is good.

The most current information on treatment of childhood ALL is available in the PDQ (Physician Data Query) on the National Cancer Institute website (http://www.cancer.gov/cancertopics/pdq/treatment/childALL/healthprofessional/).

**SUPPORTIVE CARE**

Close attention to the medical supportive care needs of the patients is essential in successfully administering aggressive chemotherapeutic programs. Patients with high white blood cell counts are especially prone to tumor lysis syndrome as therapy is initiated. The kidney failure associated with very high levels of serum uric acid can be prevented or treated with allopurinol or urate oxidase. Chemotherapy often produces severe myelosuppression, which can require erythrocyte and platelet transfusion and which always requires a high index of suspicion and aggressive empiric antimicrobial therapy for sepsis in febrile children with neutropenia. Patients must receive prophylactic treatment for *Pneumocystis jiroveci* pneumonia during chemotherapy and for several months after completing treatment.

The successful therapy of ALL is a direct result of intensive and often toxic treatment. However, such intensive therapy can incur substantial academic, developmental, and psychosocial costs for children with ALL and considerable financial costs and stress for their families. Both long-term and acute toxicity effects can occur. An array of cancer care professionals with training and experience in addressing the myriad of problems that can arise is essential to minimize the complications and achieve an optimal outcome.

**PROGNOSIS**

Improvements in therapy and risk stratification have resulted in significant increases in survival rates, with current data showing overall 5 yr survival around 90% (Fig. 495-6). However, survivors are more likely to experience significant chronic medical conditions compared to siblings, including musculoskeletal, cardiac, and neurologic conditions. Overall, long-term management following ALL should be...
conducted in a clinic where children and adolescents can be followed by a variety of specialists to address the challenges of these unique patients.

Bibliography is available at Expert Consult.

495.2 Acute Myelogenous Leukemia

David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey

EPIDEMIOLOGY

AML accounts for 11% of the cases of childhood leukemia in the United States; it is diagnosed in approximately 370 children annually. The relative frequency of AML increases in adolescence, representing 36% of cases of leukemia in 15-19 yr olds. One subtype, acute promyelocytic leukemia (APL), is more common in certain regions of the world, but the incidence of the other types is generally uniform. Several chromosomal abnormalities associated with AML have been identified, but no predisposing genetic or environmental factors can be identified in most patients (see Table 495-1). Nonetheless, a number of risk factors have been identified, including ionizing radiation, chemotherapeutic agents (e.g., alkylating agents, epipodophyllotoxin), organic solvents, paroxysmal nocturnal hemoglobinuria, and certain syndromes: Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, Li-Fraumeni syndrome, and neurofibromatosis type 1.

CELLULAR CLASSIFICATION

The characteristic feature of AML is that >20% of bone marrow cells on bone marrow aspiration or biopsy touch preparations constitute a fairly homogenous population of blast cells, with features similar to those that characterize early differentiation states of the myeloid-monocyte-megakaryocyte series of blood cells. Current practice requires the use of flow cytometry to identify cell surface antigens and use of chromosomal and molecular genetic techniques for additional diagnostic precision and to aid the choice of therapy. The WHO has proposed a new classification system that incorporates morphology, chromosome abnormalities, and specific gene mutations. This system provides significant biologic and prognostic information (Table 495-3).

CLINICAL MANIFESTATIONS

The production of symptoms and signs of AML is a result of replacement of bone marrow by malignant cells and caused by secondary bone marrow failure. Patients with AML can present with any or all of the findings associated with marrow failure in ALL. In addition, patients with AML present with signs and symptoms that are uncommon in ALL, including subcutaneous nodules or “blueberry muffin” lesions (especially in infants), infiltration of the gingiva (especially in monocytic subtypes), and laboratory findings of disseminated intravascular coagulation (especially indicative of APL), and discrete masses, known as chloromas or granulocytic sarcomas. These masses may occur in the absence of apparent bone marrow involvement and typically are associated with a t(8;21) translocation. Chloromas also may be seen in the orbit and epidural space.

DIAGNOSIS

Analysis of bone marrow aspiration and biopsy specimens of patients with AML typically reveals the features of a hypercellular marrow consisting of a monotonous pattern of cells. Flow cytometry and special stains assist in identifying myeloperoxidase-containing cells, thus confirming both the myelogenous origin of the leukemia and the diagnosis. Some chromosomal abnormalities and molecular genetic markers are characteristic of specific subtypes of disease (Table 495-4).

PROGNOSIS AND TREATMENT

Aggressive multiagent chemotherapy is successful in inducing remission in approximately 85-90% of patients. Survival has increased dramatically since the 1970s, when only 15% of newly diagnosed patients survived, compared to a current survival rate of 60-70% with modern therapy (Fig. 495-7). Targeting therapy to genetic markers may be beneficial (see Table 495-4). Up to 5% of patients die of either infection or bleeding before a remission can be achieved. Matched-sibling bone marrow or stem cell transplantation after remission achieves long-term disease-free survival in about two thirds of patients. Continued chemotherapy for patients who do not have a matched sibling donor is
Increased supportive care is needed in patients with AML because the intensive therapy they receive produces prolonged bone marrow suppression with a very high incidence of serious infections, especially Streptococcal viridans sepsis and fungal infection. These patients may require prolonged hospitalization, filgrastim (granulocyte colony-stimulating factor), and prophylactic antimicrobials.

The most current information on treatment of AML is available in the PDQ (Physician Data Query) on the National Cancer Institute website (http://www.cancer.gov/cancertopics/pdq/treatment/childAML/healthprofessional/).

Bibliography is available at Expert Consult.

### 495.3 Down Syndrome and Acute Leukemia and Transient Myeloproliferative Disorder

**David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey**

Acute leukemia occurs about 15-20 times more frequently in children with Down syndrome than in the general population (see Chapters 81 and 492). The ratio of ALL to AML in patients with Down syndrome is the same as that in the general population. The exception is during the 1st 3 yr of life, when AML is more common. In children with Down syndrome who have ALL, the expected outcome of treatment is slightly inferior to that for other children, which can be partially explained by a lack of good prognostic characteristics, such as ETV6-RUNX1 and trisomies, as well as genetic abnormalities that are associated with an inferior prognosis, such as IKZF1. Patients with Down syndrome demonstrate a remarkable sensitivity to methotrexate and other antimetabolites, which can result in substantial toxicity if standard doses are administered. In AML, however, patients with Down syndrome have much better outcomes than non–Down syndrome children, with a >80% long-term survival rate. After induction therapy, these patients receive therapy that is less intensive to achieve better results.

Approximately 10% of neonates with Down syndrome develop a transient leukemia or myeloproliferative disorder characterized by high leukocyte counts, blast cells in the peripheral blood, and associated anemia, thrombocytopenia, and hepatosplenomegaly. These features usually resolve within the 1st 3 mo of life. Although these neonates can require temporary transfusion support, they do not require chemotherapy unless there is evidence of life-threatening complications. However, patients who have Down syndrome and who develop this transient leukemia or myeloproliferative disorder require close follow-up, because 20-30% will develop typical leukemia (often acute megakaryocytic leukemia) by 3 yr of life (mean onset, 16 mo). GATA1 mutations (a transcription factor that controls megakaryopoiesis) are present in blasts from patients with Down syndrome who have
Bibliography
Imatinib (Gleevec), an agent designed specifically to inhibit the BCR-ABL tyrosine kinase, has been used in adults and children and has shown an ability to produce major cytogenetic responses in >70% of patients (see Table 494-1). Experience in children suggests it can be used safely with results comparable to those seen in adults. Second-generation tyrosine kinase inhibitors, such as dasatinib, have improved remission rates in adults and are now included in the first-line therapy in that population while they are being studied in children. While waiting for a response to the tyrosine kinase inhibitor, disabling or threatening signs and symptoms of CML can be controlled during the chronic phase with hydroxyurea, which gradually returns the leukocyte count to normal. Prolonged morphologic and cytogenetic responses are expected, but the opportunity for cure is enhanced by human leukocyte antigen–matched family donor allogeneic stem cell transplant, with up to 80% of children achieving a cure.

Bibliography is available at Expert Consult.

### 495.4 Chronic Myelogenous Leukemia

David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey

CML is a clonal disorder of the hematopoietic tissue that accounts for 2-3% of all cases of childhood leukemia. Approximately 99% of the cases are characterized by a specific translocation, t(9;22)(q34;q11), known as the Philadelphia chromosome, resulting in a BCR-ABL fusion protein.

The presenting symptoms of CML are nonspecific and can include fever, fatigue, weight loss, and anorexia. Splenomegaly also may be present, resulting in pain in the left upper quadrant of the abdomen. The diagnosis is suggested by a high white blood cell count with myeloid cells at all stages of differentiation in the peripheral blood and bone marrow and is confirmed by cytogenetic and molecular studies that demonstrate the presence of the characteristic Philadelphia chromosome and the BCR-ABL gene rearrangement. This translocation, although characteristic of CML, is also found in a small percentage of patients with ALL.

The disease is characterized by an initial chronic phase in which the malignant clone produces an elevated leukocyte count with a predominance of mature forms but with increased numbers of immature granulocytes. In addition to leukocytosis, blood counts can reveal mild anemia and thrombocytosis. Typically, the chronic phase terminates 3-4 yr after onset, when the CML moves into the accelerated or "blast crisis" phase. At this point, the blood counts rise dramatically and the clinical picture is indistinguishable from acute leukemia. Additional manifestations can occur, including neurologic symptoms from hyperleukocytosis, which causes increased blood viscosity with decreased CNS perfusion.

Bibliography is available at Expert Consult.

### 495.5 Juvenile Myelomonocytic Leukemia

David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey

JMML, formerly termed juvenile CML, is a clonal proliferation of hematopoietic stem cells that typically affects children younger than 2 yr of age. JMML is rare, constituting <1% of all cases of childhood leukemia. Patients with this disease do not have the Philadelphia chromosome that is characteristic of CML. Patients with JMML present with rashes, lymphadenopathy, splenomegaly, and hemorrhagic manifestations. Analysis of the peripheral blood often shows an elevated leukocyte count with increased monocytes, thrombocytopenia, and anemia with the presence of erythroblasts. The bone marrow shows a myelodysplastic pattern, with blasts accounting for <20% of cells. Most patients with JMML have been found to have mutations that lead to activation of the RAS oncogene pathway including NFI and PTPN11. Patients with neurofibromatosis type 1 and Noonan syndrome have a predilection for this type of leukemia, since they have germline mutations involved in RAS signaling. Therapeutic reports are largely anecdotal. Stem cell transplantation offers the best opportunity for cure but much less so than for classic CML.

Bibliography is available at Expert Consult.

### 495.6 Infant Leukemia

David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey

Approximately 2% of cases of leukemia during childhood occur before the age of 1 year. In contrast to older children, the ratio of ALL to AML is 2:1. Leukemic clones have been noted in cord blood at birth before symptoms appear, and in 1 case the same clone was noted in maternal cells (maternal to fetal transmission). Chromosome translocations can also occur in utero during fetal hematopoiesis, thus leading to malignant clone formation.

Several unique biologic features and a particularly poor prognosis are characteristic of ALL during infancy. More than 80% of the cases demonstrate rearrangements of the MLL gene, found at the site of the 11q23 band translocation, the majority of which are the t(4;11). This subset of patients largely accounts for the very high relapse rate. These patients often present with hyperleukocytosis and extensive tissue infiltration producing organomegaly, including CNS disease. Subcutaneous nodules, known as leukemia cutis, and tachypnea caused by diffuse pulmonary infiltration by leukemic cells are observed more often in infants than in older children. The leukemic cell morphology is usually that of large irregular lymphoblasts, with a phenotype...


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negative for the CD10 (common ALL antigen) marker (pro-B) unlike most older children with B-ALL who are CD10+.

Very intensive chemotherapy programs, including stem cell transplantation, are being explored in infants with MLL gene rearrangements, but none has yet proved satisfactory. Infants with leukemia who lack the 11q23 rearrangements have a prognosis similar to that of older children with ALL.

Infants with AML often present with CNS or skin involvement and have a subtype known as acute myelomonocytic leukemia. The treatment may be the same as that for older children with AML, with similar outcome. Meticulous supportive care is necessary because of the young age and aggressive therapy needed in these patients.

Bibliography is available at Expert Consult.
Bibliography


Lymphoma is the third most common cancer among U.S. children (age 14 yr or younger), with an annual incidence of 15 cases per 1 million children. It is the most common cancer in adolescents, accounting for >25% of newly diagnosed cancers in persons 15-19 yr old. The 2 broad categories of lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), have different clinical manifestations and treatments.*

496.1 Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a malignant process involving the lymphoreticular system that accounts for 6% of childhood cancers. In the United States, HL accounts for approximately 5% of cancers in persons 14 yr of age or younger; it accounts for approximately 15% of cancers in adolescents (15-19 yr of age), making HL the most common malignancy in this age group.

EPIDEMIOLOGY

The worldwide incidence of HL is approximately 2-4 new cases/100,000 population/yr; there is a bimodal age distribution, with peaks at 15-35 yr of age and again after 50 yr. It is the most common cancer seen in adolescents and young adults, and the third most common in children younger than the age of 15 yr. In developing countries, the early peak tends to occur prior to adolescence. A male:female predominance is found among young children, but lessens with age. Infectious agents may be involved, such as human herpesvirus 6, cytomegalovirus, and Epstein-Barr virus (EBV). The role of EBV is supported by prospective serologic studies. Infection with EBV confers a 4-fold higher risk of developing HL and may precede the diagnosis by years. EBV antigens have been demonstrated in HL tissues, particularly type II latent membrane proteins 1 and 2, although EBV status is not thought to be prognostic of outcome.

PATHOGENESIS

The Reed-Sternberg (RS) cell, a pathognomonic feature of HL, is a large cell (15-45 μm in diameter) with multiple or multilobulated nuclei. This cell type is considered the hallmark of HL, although similar cells are seen in infectious mononucleosis, NHL, and other conditions. The RS cell is clonal in origin and arises from the germinal center B cells but typically has lost most B-cell gene expression and function. There is no single simple genetic aberration that leads to malignant transformation of the RS cell, but rather a combination of somatic mutations, chromosomal instability, and complex chromosomal rearrangements have been reported with no particular pattern or frequency. This typically leads to cell regulation defects such as constitutive activation of the nuclear factor-κB pathway or abnormal regulation of the Bcl-2 family of proteins. HL is characterized by a variable number of RS cells surrounded by an inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils in different proportions, depending on the HL histologic subtype. The interaction between the RS cell and these background inflammatory cells with their associated cytokine release is important in the development and progression of HL. Reactive infiltration of eosinophils and CD68+ macrophages, and increased concentrations of cytokines, such as interleukins 1 and 6 and tumor necrosis factor, are all associated with an unfavorable prognosis, including advanced stage, the presence of “B” symptoms, decreased response to therapy, and reduced survival. In addition, evidence of CD8+ T cells surrounding the RS cell offers evidence of an important role in T-cell promotion of malignant cell survival, perhaps through the CD30 and CD40 ligands found on RS cells. Other features that distinguish the histologic subtypes include various degrees of fibrosis and the presence of collagen bands, necrosis, or malignant reticular cells (Fig. 496-1). The distribution of subtypes varies with age.

The Revised World Health Organization Classification of Lymphoid Neoplasms (Table 496-1) includes 2 modifications of the older Rye system. HL appears to arise in lymphoid tissue and spread to adjacent lymph node areas in a relatively orderly fashion. Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow, or brain, and is usually associated with systemic symptoms.

CLINICAL MANIFESTATIONS

Patients commonly present with painless, nontender, firm, rubbery, cervical or supraclavicular lymphadenopathy and usually some degree of mediastinal involvement. Clinically detectable hepatosplenomegaly is rarely encountered. Depending on the extent and location of nodal and extranodal disease, patients may present with symptoms and signs of airway obstruction (dyspnea, hypoxia, cough), pleural or pericardial effusion, hematocellular dysfunction, or bone marrow infiltration (anemia, neutropenia, or thrombocytopenia). Disease manifesting below the diaphragm is rare and occurs in approximately 3% of all cases. Systemic symptoms, classified as B symptoms that are considered important in staging, are unexplained fever >38°C (100.4°F), weight loss >10% total body weight over 6 mo, and drenching night sweats. Less common and not considered of prognostic significance are symptoms of pruritus, lethargy, anorexia, or pain that worsens after ingestion of alcohol. Patients also exhibit immune system abnormalities that often persist during and after therapy.

DIAGNOSIS

Any patient with persistent, unexplained lymphadenopathy unassociated with an obvious underlying inflammatory or infectious process should undergo chest radiography to identify the presence of a large mediastinal mass before undergoing lymph node biopsy. Formal excisional biopsy is preferred over needle biopsy to ensure that adequate tissue is obtained, both for light microscopy and for appropriate immunohistochemical and molecular studies. Once the diagnosis of HL is established, extent of disease (stage) should be determined to allow selection of appropriate therapy (Table 496-2). Evaluation includes history, physical examination, and imaging studies, including chest radiograph; CT scans of the neck, chest, abdomen, and pelvis; and positron emission tomography (PET) scan. Laboratory studies should include a complete blood cell count to identify abnormalities that might suggest marrow involvement; erythrocyte sedimentation rate; and measurement of serum ferritin, which is of some prognostic

*The views expressed are the result of independent work and do not necessarily represent the views or findings of the U.S. Food and Drug Administration or the United States.
Figure 496-1 Histologic subtypes of Hodgkin lymphoma. A, Hematoxylin & eosin stains of nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) demonstrating a nodular proliferation with a moth-eaten appearance. B, High-power view demonstrating the neoplastic L and H cells found in NLPHL. C, Classic Hodgkin lymphoma, nodular sclerosis subtype. Large mononuclear and binucleate Reed-Sternberg cells are seen admixed in the inflammatory cell background. D, Classic Hodgkin lymphoma, mixed cellularity subtype, demonstrating increased numbers of Reed-Sternberg cells in a mixed inflammatory background without sclerotic changes. E, High-power view of a classic Reed-Sternberg cell showing binucleate cells with prominent eosinophilic nucleoli and relatively abundant cytoplasm. F, Few CD68+ macrophages in a treatment success patient. G, Many CD68+ macrophages in a treatment failure patient.

Table 496-1 New World Health Organization/Revised European–American Classification of Lymphoid Neoplasms Classification System for Hodgkin Lymphoma

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<th>Subtype</th>
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<td>Lymphocyte rich</td>
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<td>Mixed cellularity</td>
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<td>Nodular sclerosis</td>
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</table>


significance and, if abnormal at diagnosis, serves as a baseline to evaluate the effects of treatment. A chest radiograph is particularly important for measuring the size of the mediastinal mass in relation to the maximal diameter of the thorax (Fig. 496-2). This determines “bulk” disease and becomes prognostically significant. Chest CT more clearly defines the extent of a mediastinal mass if present and identifies hilar nodes and pulmonary parenchymal involvement, which may not be evident on chest radiographs. Bone marrow aspiration and biopsy should be performed to rule out advanced disease. Bone scans are performed in patients with bone pain and/or elevation of alkaline phosphatase. Gallium scan can be particularly helpful in identifying areas of increased uptake, which can then be reevaluated at the end of treatment. Fluorodeoxyglucose PET imaging has advantages over gallium scanning, as it is a 1-day procedure with higher resolution, better dosimetry, less intestinal activity, and the potential to quantify disease. PET scans are being evaluated as a prognostic tool in HL, enabling therapy to be reduced in those predicted to have a good outcome.

The staging classification currently used for HL was adopted at the Ann Arbor Conference in 1971 and was revised in 1989 (see Table 496-2). HL can be subclassified into A or B categories: A is used to identify asymptomatic patients and B is for patients who exhibit any B symptoms. Extralymphatic disease resulting from direct extension of an involved lymph node region is designated by category E. A complete response in HL is defined as the complete resolution of disease on clinical examination and imaging studies or at least 70-80% reduction of disease and a change from initial positivity to negativity on either gallium or PET scanning because residual fibrosis is common.

TREATMENT

Multiple agents allow different mechanisms of action to have non-overlapping toxicities so that full doses can be given to each patient.
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Chemotherapy and radiation therapy are both effective in the treatment of HL. Treatment of HL in pediatric patients is risk adapted and involves the use of combined chemotherapy with or without low-dose involved-field radiation therapy based on response. Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of bulky nodal disease. Radiation therapy alone, once given at higher doses, initially resulted in prolonged remission and cure rates in patients with low-stage HL. However, this treatment also caused significant long-term morbidity in pediatric patients, including growth retardation, thyroid dysfunction, and cardiac and pulmonary toxicity. The development of effective multiagent combination chemotherapy was a major milestone in the treatment of HL resulting in a complete response rate of 70-80% and cure rate of 40-50% in patients with advanced-stage disease. However, this regimen also led to significant acute and long-term toxicity. The desire to reduce side effects and morbidity has stimulated attempts to reduce the intensity of chemotherapy as well as radiation dose and volume. Newer combinations of chemotherapy have reduced the risk of secondary cancers. Also, current radiation therapy utilizes lower amounts of overall radiation in addition to narrowing the radiation treatment field to either involved-field or even involved-node irradiation. The current Children's Oncology Group trials are investigating whether radiation therapy can be eliminated altogether in patients who have a very good rapid early response to pre-radiation induction chemotherapy.

Chemotherapy agents commonly used to treat children and adolescents with HL include cyclophosphamide, procarbazine, vincristine or vinblastine, prednisone or dexamethasone, doxorubicin, bleomycin, dacarbazine, etoposide, methotrexate, and cytosine arabinoside. The combination chemotherapy regimens in current use are based on COPP (cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone) or ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine), with the addition of prednisone, cyclophosphamide, and etoposide (ABVE-PC and BEACOPP) or BAVD (brentuximab vedotin, doxorubicin [Adriamycin], vincristine, dacarbazine) in various combinations for intermediate- and high-risk groups (Table 496-3). “Risk-adapted” protocols are based on both staging criteria and rapidity of response to initial chemotherapy. The aim is to reduce total drug doses and treatment duration and to eliminate radiation therapy if possible.

Agents such as those that disrupt the nuclear factor-κB pathway or monoclonal antibodies that target RS tumor cells as well as the benign reactive cells that surround them are currently being investigated. Ongoing clinical trials report encouraging results with the use of anti-CD20 antibody (rituximab), particularly in nodular lymphocyte-predominant Hodgkin lymphoma where trials in relapsed disease have shown an overall response rate of 94%. In addition, anti-CD30 agents

![Figure 496-2](image-url)

**Figure 496-2** A, Anterior mediastinal mass in a patient with Hodgkin disease before therapy. B, After 2 mo of chemotherapy, the mediastinal mass has disappeared.

<table>
<thead>
<tr>
<th>CHEMOTHERAPY REGIMEN</th>
<th>CORRESPONDING AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD</td>
<td>Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine</td>
</tr>
<tr>
<td>ABVD-Rituxan</td>
<td>Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine, rituximab</td>
</tr>
<tr>
<td>ABVD</td>
<td>Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine</td>
</tr>
<tr>
<td>ABVE (DBVE)</td>
<td>Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide</td>
</tr>
<tr>
<td>VAMP</td>
<td>Vincristine, doxorubicin (Adriamycin), methotrexate, prednisone</td>
</tr>
<tr>
<td>OPPA ± COPP (females)</td>
<td>Vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine</td>
</tr>
<tr>
<td>OEPA ± COPP (males)</td>
<td>Vincristine (Oncovin), etoposide, prednisone, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine</td>
</tr>
<tr>
<td>COPP/ABV</td>
<td>Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), bleomycin, vinblastine</td>
</tr>
<tr>
<td>BEACOPP (advanced stage)</td>
<td>Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine</td>
</tr>
<tr>
<td>COPP</td>
<td>Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine</td>
</tr>
<tr>
<td>CHOP</td>
<td>Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), prednisone</td>
</tr>
<tr>
<td>ABVE-PC (DBVE-PC)</td>
<td>Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, cyclophosphamide</td>
</tr>
<tr>
<td>ICE ± (Brentuximab)</td>
<td>Ifosfamide, carboplatin, etoposide ± brentuximab</td>
</tr>
<tr>
<td>Ifos/Vino ± (Brentuximab)</td>
<td>Ifosfamide, vinorelbine ± brentuximab</td>
</tr>
</tbody>
</table>
are being used that are targeted to the RS cells themselves, where CD30 is abundantly expressed. Brentuximab vedotin is an antibody–drug conjugate that is now FDA approved to treat Hodgkin lymphoma. It combines the chimeric anti-CD30 antibody brentuximab linked to the antimitotic agent monomethyl auristatin E. This agent shows impressive efficacy as single-agent therapy in refractory HL and is currently being tested as part of upfront therapy combined with chemotherapy in patients with newly diagnosed disease. EBV-specific cytotoxic T lymphocytes (CTLs) can also be generated from allogeneic donors for patients with advanced HL (Fig. 496–3). In clinical trials, these show promising results, with enhanced antiviral activity and stabilization of disease even though all patients continue to have persistent disease. EBV-CTLs have been developed and are currently being investigated. These enhanced EBV-CTLs are designed to be latent membrane protein 1/2 specific and can be generated from second (in the case of bone marrow transplant recipients) or even third-party donors for patients with refractory disease. These newer approaches represent an exciting new direction in adoptive cellular tumor immunology, and it remains to be determined whether CTLs will have improved cytotoxicity that can overcome inhibitory signals.

**RELAPSE**

Most relapses occur within the 1st 3 yr after diagnosis, but relapses as late as 10 yr have been reported. Relapse cannot be predicted accurately with this disease. Poor prognostic features include tumor bulk, stage at diagnosis, extralymphatic disease, and presence of B symptoms. Patients who achieve an initial chemosensitive response but relapse or progress less than 12 mo from diagnosis are candidates for myeloablative chemotherapy and autologous stem cell transplantation with or without the addition of radiation therapy. Retrospective studies show a significant decrease in relapse in patients with HL following autologous vs autologous stem cell transplant (18% vs 41%). Although in earlier studies there was no improvement in overall survival owing to a high transplantation-related mortality, reduced-intensity conditioning or nonmyeloablative regimens are successful at reducing regimen-related morbidity and mortality associated with myeloablative allogeneic stem cell transplantation while still achieving a strong graft-versus-HL effect. For more difficult-to-treat refractory cases, agents such as Zevalin or Bexxar are being trialed, often in combination with stem cell transplantation strategies. Both are monoclonal anti-CD20 antibodies to which a radioactive isotope is directly linked. Clinical trials show each to be more effective than rituximab in NHL patients, and there is some interest in studying their use in the CD20 subpopulation of HL patients.

**PROGNOSIS**

With the use of current therapeutic regimens, patients with favorable prognostic factors and early-stage disease have an event-free survival (EFS) of 85-90% and an overall survival (OS) at 5 yr of >95%. Patients with advanced-stage disease have slightly lower EFS (80-85%) and OS (90%), respectively, although OS has approached 100% with dose-intensive chemotherapy (Table 496–4). Prognosis after relapse depends

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**Figure 496-3** Epstein-Barr virus (EBV)–specific cytotoxic T lymphocyte (CTL) production. EBV-transformed B-cell lymphoblastoid cell line (LCLs) are prepared from the CTL donor by infection of peripheral blood mononuclear cells (PBMCs) with a clinical-grade laboratory strain of EBV (B95-8) in the presence of cyclosporine. Once the LCL is established (about 6 wk), it is irradiated and used to stimulate PBMCs from the same donor at a 40:1 ratio of PBMC:LCL. From 9-12 days later and weekly thereafter, the T cells are restimulated with the LCL at a 4:1 ratio. Interleukin 2 is added 3 days after the second stimulation and twice weekly thereafter. The CTLs should kill autologous LCLs but not autologous phytohemagglutinin blasts. Their specificity is donor dependent and they may have specificity for any of the 10 latency-associated antigens and/or for early lytic cycle proteins that are expressed by a small fraction of the LCLs, which are grown in acyclovir to prevent the production of infectious virus by blocking the viral thymidine kinase. (Adapted from Bollard CM, Rooney CM, Heslop HE. T-cell therapy in the treatment of post-transplant lymphoproliferative disease. Nat Rev Clin Oncol 9:510–519, 2012, Fig. 2.)

**Table 496-4** Treatment Regimens and Outcome by Disease Staging

<table>
<thead>
<tr>
<th>Localized/Low Stage</th>
<th>Intermediate</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hodgkin lymphoma</strong></td>
<td><strong>POG study 9426/GPOH-HD 95: ABVD-type therapy ± IFRT (risk adapted based on early response to chemotherapy)</strong></td>
<td><strong>Stanford/DAL-HD-90: COPP-based or dose-intensive multiagent chemotherapy + low-dose RT</strong></td>
</tr>
<tr>
<td><strong>POG 9426/CCG 5942: ABVD-type therapy ± IFRT (risk adapted)</strong></td>
<td><strong>HD9/HD12/CCG 59704: Dose-intensive BEACOPP ± IFRT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>POG 8725/DAL-HD-90: Dose-intensive multiagent chemotherapy + low-dose RT</strong></td>
<td><strong>POG 8725: 5-yr EFS: 72-89% (age based)</strong></td>
<td><strong>HD9/HD12/CCG 59704: 5 yr EFS/OS: 88-93%/~100%</strong></td>
</tr>
<tr>
<td><strong>HD9/HD12/CCG 59704: Dose-intensive BEACOPP ± IFRT</strong></td>
<td><strong>5 yr OS: 85-90%</strong></td>
<td><strong>5 yr OS: 85-90%</strong></td>
</tr>
<tr>
<td><strong>HD9/HD12/CCG 59704: Dose-intensive BEACOPP ± IFRT</strong></td>
<td><strong>5 yr EFS: 86%</strong></td>
<td><strong>5 yr EFS: 86%</strong></td>
</tr>
<tr>
<td><strong>5 yr OS: 95%</strong></td>
<td><strong>5 yr OS: 95%</strong></td>
<td><strong>5 yr OS: 95%</strong></td>
</tr>
</tbody>
</table>

**Table 496-4** Treatment Regimens and Outcome by Disease Staging

- **LOCALIZED/LOW STAGE**: EBV-LCL PBMC > 5 weeks → EBV LCL 3-6 weeks
- **INTERMEDIATE**: R:S ratio 40:1 IL-2 IL-2 IL-2 IL-2 IL-2
- **ADVANCED**: EBV-specific CTL
on the time from completion of treatment to recurrence, site of relapse (nodal vs extranodal), and presence of B symptoms at relapse. Patients whose disease relapses >12 mo after chemotherapy alone or combined-modality therapy have the best prognosis, and their relapses usually respond to additional standard therapy, resulting in a long-term survival of 60-70%. A myeloablative autologous stem cell transplantation in patients with refractory disease or relapse within 12 mo of therapy results in a long-term survival rate of only 40-50%. Allogeneic stem cell transplantation has shown promise in patients with poor risk features at relapse/progression.

Bibliography is available at Expert Consult.

496.2 Non-Hodgkin Lymphoma

Jessica Hochberg, Lisa Giulino-Roth, and Mitchell S. Cairo

Non-Hodgkin lymphoma (NHL) accounts for approximately 60% of lymphomas in children and is the second most common malignancy in patients age 15-35 yr. The annual incidence of pediatric NHL in the United States is 750-800 cases/yr. In contrast to adult NHL, which is typically indolent, pediatric NHL is usually high grade and aggressive. Although more than 70% of patients present with advanced disease, the prognosis has improved dramatically, with survival rates of 90-95% for localized disease and 70-95% with advanced disease.

**EPIDEMIOLOGY**

Although most children and adolescents with NHL present with de novo disease, a small number of patients have NHL secondary to specific etiologies, including inherited or acquired immune deficiencies (e.g., severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome), viruses (e.g., HIV, EBV), and as part of genetic syndromes (e.g., ataxia-telangiectasia, Bloom syndrome). However most children in North America and Europe in whom NHL develops have no obvious genetic or environmental etiology.

**PATHOGENESIS**

The 4 major pathologic subtypes of childhood and adolescent NHL are lymphoblastic lymphoma (LBL), Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and anaplastic large cell lymphoma (ALCL). These subtypes differ in their clinical presentation, biological characteristics, and therapeutic response. The etiology of NHL is often multifactorial, involving genetic and environmental factors.

### Table 496-4 Treatment Regimens and Outcome by Disease Staging—cont’d

<table>
<thead>
<tr>
<th>Localized/Low Stage</th>
<th>Intermediate</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burkitt lymphoma and diffuse large B-cell lymphoma</strong></td>
<td><strong>FAB/LMB 96 Group A therapy:</strong> Complete surgical resection followed by 2 cycles of chemotherapy</td>
<td><strong>FAB/LMB 96 Group B therapy</strong> with reduced cyclophosphamide and no maintenance therapy; <strong>COG ANHL01P1:</strong> FAB/LMB Group B therapy + rituximab</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td><strong>4 yr EFS:</strong> 99% (CI 94-99.5%); 4 yr OS: 99% (CI 96-99.9%)</td>
<td><strong>4 yr EFS:</strong> 92% (CI 90-94%); 4 yr OS: 95% (CI 93-96%); <em>PMB DLBCL has worse prognosis (EFS/OS: 66/73%); COG ANHL01P1:</em>* 3 yr EFS 93% (CI 79-98%); 3 yr OS 95% (CI 83-99%)</td>
</tr>
<tr>
<td><strong>Lymphoblastic lymphoma</strong></td>
<td><strong>NHL-BFM86/90/95:</strong> COG AS971: ALL-type therapy × 2 yr without prophylactic cranial RT</td>
<td><strong>No intermediate group:</strong> disease classified as localized (stages I/II) or advanced (stages III/IV)</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td><strong>COG AS971:</strong> 5 yr EFS: 90% (CI 78-96%); 5 yr OS: 96% (CI 84-99%)</td>
<td><strong>No intermediate group:</strong> disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)</td>
</tr>
<tr>
<td><strong>Anaplastic large cell lymphoma</strong></td>
<td><strong>EICHNL ALCL 99:</strong> Short intensive chemotherapy + HD MTX</td>
<td><strong>EICHNL database:</strong> 5 yr PFS: 89% (CI 82-96%); 5 yr OS: 94% (CI 89-99%)</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td><strong>EICHNL database:</strong> 5 yr PFS: 89% (CI 82-96%); 5 yr OS: 94% (CI 89-99%)</td>
<td><strong>No intermediate group:</strong> disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)</td>
</tr>
</tbody>
</table>

**Legend:**
- ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; BM, bone marrow (involvement); CCG, Children’s Cancer Group; CI, 95% confidence interval; CNS, central nervous system (involvement); COG, Children’s Oncology Group; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; CRT, chemoradiotherapy; EFS, event-free survival; EICHNL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB, French-American-British; HD MTX, high-dose methotrexate; IFRT, involved field radiation therapy; LMB, Lymphome Malins de Burkit; MTX, methotrexate; NHL-BFM, non-Hodgkin lymphoma Berlin-Frankfurt-Munster; OS, overall survival; PFS, progression-free survival; PMB DLBCL, primary mediastinal B-cell diffuse large B-cell lymphoma; POG, Pediatric Oncology Group; px, prophylactic; RT, radiation therapy.
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Bibliography

lymphoma (ALCL; Figs. 496-4 and 496-5). LBL arises from immature B or T lymphocytes whereas BL, DLBCL, and ALCL are mature B- or T-cell neoplasms. DLBCL is further divided into several subtypes: the germinal center B-cell–like, which carries a favorable prognosis and accounts for the vast majority of pediatric cases of DLBCL, and the subtypes with poorer prognosis, activated B-cell–like and primary mediastinal B-cell subtypes. The cell of origin varies among NHL histologic subtypes. Almost all BLs and DLBCLs are of B-cell origin; 90% of cases of LBL are of T-cell origin and 10% of B-cell origin; and 70% of cases of ALCL are of T-cell origin, 20% are of null-cell origin, and 10% are of B-cell origin. Cellular surface markers can aid in differentiating NHL subtypes and also present opportunities for targeted treatments. BL and DLBCL frequently express the B-cell antigens CD19, CD20, and CD22. ALCL, in contrast, expresses the CD30 antigen. Some pathologic subtypes have specific cytogenetic aberrations. Children with BL commonly have a t(8;14) translocation (90%) or, less commonly, a t(2;8) or t(8;22) translocation (10%). Children with BL who have a 13q deletion or complex karyotype have a poor prognosis. Those with DLBCL may have a t(8;14) translocation (30%) and often have a complex (80%) and aneuploid (80%) karyotype. Patients with ALCL commonly have a t(2;5) translocation (90%), which results in the formation of a fusion gene encoding the constitutively active nucleophosmin-anaplastic lymphoma kinase tyrosine kinase. Variant anaplastic lymphoma kinase (ALK) translocations, all with a breakpoint at 2p23, have also been reported. T-cell LBL harbors many of the same cytogenetic abnormalities as T-cell acute lymphoblastic leukemia (T-ALL), including rearrangements with breakpoints at 14q11.2 involving the T-cell receptor, and t(5;14) translocation (20%), which does not involve the 14q11.2 breakpoint.

Genomic studies have offered insights into NHL pathogenesis as well as elucidated potential targets for novel therapies. Gene expression profiling of T-LBL and T-ALL has implicated the activation of oncogenic transcription factors as a result of aberrant T-cell receptor gene rearrangement. One of the most frequently activated signaling pathways is NOTCH1, which may be amenable to therapeutic targeting with γ-secretase inhibitors. In BL and DLBCL, extensive genomic work has identified unique gene expression signatures that differentiate these 2 mature B-cell neoplasms. In addition, next-generation sequencing of BL has identified genetic lesions in TCF3 and ID3, which lead to activation of the AKT/PI3 kinase pathway. Other genetic lesions that have been described in BL include loss of function of the chromatin remodeling genes ARID1A and SMARCA4. Importantly, many of these alterations are potentially targetable by agents that are currently in development.

**CLINICAL MANIFESTATIONS**

The clinical manifestations of childhood and adolescent NHL depend primarily on pathologic subtype and sites of involvement. The staging system used for NHL is the St. Jude/Murphy classification (Table 496-5), although this classification schema is currently under an
Lymphoma

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Table 496-5  St. Jude Staging System for Childhood Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen</td>
</tr>
<tr>
<td>II</td>
<td>A single tumor (extranodal) with regional node involvement Two or more nodal areas on the same side of the diaphragm Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, which must be grossly (&gt;90%) resected</td>
</tr>
<tr>
<td>III</td>
<td>Two single tumors (extranodal) on opposite sides of the diaphragm Two or more nodal areas above and below the diaphragm Any primary intrathoracic tumor (mediastinal, pleural, or thymic) Any extensive primary intraabdominal disease</td>
</tr>
<tr>
<td>IV</td>
<td>Any of the above, with initial involvement of central nervous system or bone marrow at time of diagnosis</td>
</tr>
</tbody>
</table>


Table 496-6  Risk Stratification Groups for Pediatric B-Cell NHL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Berlin-Frankfurt-Munster (BFM) French-American-British (FAB)</td>
</tr>
<tr>
<td>R1</td>
<td>Resected stage I and abdominal completely resected</td>
</tr>
<tr>
<td>R2</td>
<td>Stage I or II, not resected Stage III with LDH &lt;500 U/L</td>
</tr>
<tr>
<td>R3</td>
<td>Stage III with LDH ≥500 to &lt;1000 U/L or Stage IV with LDH &lt;1000 U/L and CNS-negative</td>
</tr>
<tr>
<td>R4</td>
<td>Stage III or IV with LDH ≥1000 U/L and/or CNS-positive</td>
</tr>
<tr>
<td>Group A</td>
<td>Resected stage I and abdominal completely resected stage II</td>
</tr>
<tr>
<td>Group B</td>
<td>All patients not in Group A or C</td>
</tr>
<tr>
<td>Group C</td>
<td>Bone marrow disease (≥25% L3 blasts) and/or CNS-positive</td>
</tr>
</tbody>
</table>

Low Risk:
- Berlin-Frankfurt-Munster (BFM)
- French-American-British (FAB)

High Risk:
- Resected stage I and abdominal completely resected
- Stage I or II, not resected
- Stage III with LDH <500 U/L
- Stage IV with LDH <1000 U/L and CNS-negative
- Stage III or IV with LDH ≥1000 U/L and/or CNS-positive

NHL can present as a life-threatening oncologic emergency. These manifestations are important to recognize as they require intensive supportive care and, in some cases, alternative treatment. Superior mediastinal syndrome can occur as a consequence of a large mediastinal mass causing obstruction of blood flow or respiratory airways. Spinal cord tumors can cause cord compression and acute paraplegias requiring emergent radiation therapy. Lastly, tumor lysis syndrome (TLS) can occur from rapid cell turnover, which is especially common in BL. TLS can result in severe metabolic abnormalities including hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. This can rapidly lead to renal insufficiency/failure as well as cardiac abnormalities if not aggressively treated.

LABORATORY FINDINGS

Recommended laboratory and radiologic testing includes complete blood cell count; measurements of electrolytes, lactate dehydrogenase, uric acid, calcium, phosphorus, blood urea nitrogen, creatinine, bilirubin, alanine aminotransferase, and aspartate aminotransferase; bone marrow aspiration and biopsy; lumbar puncture with cerebrospinal fluid cytology, cell count and protein; chest radiographs; and neck, chest, abdominal, and pelvic CT scans (head CT for suspicion of CNS disease), and PET scan. Tumor tissue (i.e., biopsy, bone marrow, cerebrospinal fluid, or pleurocentesis/paracentesis fluid) should be tested by flow cytometry for immunophenotypic origin (T, B, or null) and cytogenetics (karyotype). Additional tests might include fluorescent in situ hybridization or quantitative reverse transcription polymerase chain reaction for specific genetic translocations, T- and B-cell gene rearrangement studies, and molecular profiling by oligonucleotide microarray.

TREATMENT

The primary modality of treatment for childhood and adolescent NHL is multiagent systemic chemotherapy with intrathecal chemotherapy (see Table 496-4). Surgery is used mainly for diagnosis. Radiation therapy is used only in special circumstances, such as CNS involvement in LBL or, in the presence of acute superior mediastinal syndrome or paraplegias. Newly diagnosed patients, especially those with BL and LBL, are at high risk for TLS. These patients require vigorous hydration, frequent electrolyte monitoring, and either a xanthine oxidase inhibitor (allopurinol, 10 mg/kg/day PO divided into 3 doses daily) or recombinant urate oxidase (rasburicase, 0.2 mg/kg/day IV once daily for up to 5 days). Recombinant urate oxidase is preferred in patients with a high risk of tumor lysis. Frequently, only a single dose is needed; however, repeat doses can be given if a subsequent rise in uric acid is seen.

Burkitt Lymphoma and Diffuse Large B-cell Lymphoma

Pediatric BL and DLBCL are treated with similar chemotherapy regimens, which are designed for mature B-NHL. Regimens vary based on stage and risk stratification. For patients with localized disease, multiagent chemotherapy is given over a 6 wk to 6 mo period and the prognosis is excellent. In the international FAB/LMB 96 (French-American-British Lymphoma, mature B cell) trial, patients with...
localized, completely resected disease received 2 cycles of COPAD (cyclophosphamide, vincristine, prednisone, and doxorubicin) resulting in a 4 yr OS of 99%. Advanced disease is usually treated with a 4-6 mo regimen of multiagent chemotherapy, such as FAB/LMB 96 protocol therapy or NHL-BFM (Berlin-Frankfurt-Munich) 95 protocol therapy with an OS of 79-90%. A subset of patients that likely require a different treatment approach are those with primary mediastinal B-cell lymphoma (PMBCL). PMBCL is a histologic subtype that represents 2% of mature B-NHLs. Pediatric patients with PMBCCL have an inferior outcome when treated with standard mature B-NHL protocols (EFS of only 66%). Alternative treatment strategies, including rituximab and other novel agents, may be of benefit to this group.

Rituximab is a monoclonal antibody directed at CD20 that improves outcomes in adult patients with B-NHL. As nearly all pediatric BLs and DLBCLs express CD20, rituximab has been examined in pediatric B-NHL; however, the efficacy in this setting is not yet known. A window study of rituximab given to pediatric patients with newly diagnosed BL and DLBCL demonstrated its activity as a single agent with a response rate of 41%. Additionally, a Children's Oncology Group study examined the safety and pharmacokinetics of rituximab when added to standard chemotherapy for intermediate-risk patients. Rituximab was found to be safe, and survival in this cohort was the best reported to date (3 yr OS of 95%). In a similar cohort of CNS-positive patients, the addition of rituximab to the chemotherapy backbone resulted in a 93% EFS.

Lymphoblastic Lymphoma
Localized or advanced LBL requires 12-24 mo of therapy including chemotherapy, intrathecal therapy, and cranial radiation in some cases. The best results in advanced LBL have been obtained using the NHL-BFM 90 protocol, which uses therapeutic approaches similar to those for childhood acute leukemia, including induction, consolidation, interim maintenance, and reinduction (advanced disease only) phases as well as a year-long maintenance phase with 6-mercaptopurine and methotrexate. Studies have attempted to determine whether cranial radiation can be omitted, with promising results; however, the sample size in these studies is small. For patients with relapsed disease, the outcome is poor (OS of 10%) and novel treatments are needed. Nelarabine is a purine analog with significant T-lymphocyte toxicity; nelarabine has been investigated in T-LBL. Nelarabine is currently undergoing investigation in high-risk patients with T-ALL and T-LBL.

Anaplastic Large Cell Lymphoma
For patients who present with localized disease, surgical resection alone is sufficient. The majority of patients, however, have advanced disease, which requires multiagent chemotherapy. Various chemotherapy regimens have been studied with similar outcomes and survival ranging from 70-79%. CNS prophylaxis consists of intrathecal chemotherapy; however, it may be possible to omit this with the substitution of high-dose methotrexate. CNS disease, although rare, can be seen and is treated with intrathecal chemotherapy and cranial radiation.

Two novel targeted agents have shown substantial promise in early-phase trials in ALCL. The CD30 antibody–drug conjugate brentuximab and the ALK inhibitor crizotinib both have impressive activity and minimal toxicity in patients with relapsed ALCL. Given the high efficacy and low toxicity profile, it may be possible to use these agents in newly diagnosed patients to eliminate the reliance on and toxicity of conventional chemotherapy.

Relapsed Non-Hodgkin Lymphoma
Patients with NHL in whom progressive or relapsed disease develops require reinduction chemotherapy and either allogeneic or autologous stem cell transplantation (SCT). The specific reinduction regimen or transplantation type depends on the pathologic subtype, previous therapy, site of recurrence, and stem cell donor availability. Although there are no randomized trials examining autologous vs allogeneic SCT for relapsed NHL, data from retrospective studies suggest that outcomes are similar with the exception of LBL and ALCL where allogeneic SCT is superior, perhaps because of a graft-vs-lymphoma effect.

As relapsed NHL can be difficult to treat, efforts have been made to identify those patients at higher risk of relapse to tailor the initial therapy. The measurement of minimal residual disease may serve as a prognostic marker and aid in risk stratification. Minimal residual disease is prognostic in ALCL and LBL. In ALCL, there is also evidence that a humoral response to the ALK kinase can be used to predict outcome with a superior outcome in patients who mount an antibody titer to ALK. Minimal residual disease measurement in intermediate-risk B-NHL is feasible and is currently being evaluated in an international trial.

Complications
Patients receiving multiagent chemotherapy for advanced disease are at acute risk for serious mucositis, infections, cytophenias that require red blood cell and platelet blood product transfusions, electrolyte imbalances, and poor nutrition. Long-term complications include the risk of growth retardation, cardiac toxicity, gonadal toxicity with infertility, and secondary malignancies.

Prognosis
The prognosis is excellent for most forms of childhood and adolescent NHL (see Table 496-4). Patients with localized disease have a 90-100% chance of survival, and those with advanced disease have a 70-95% chance of survival. As outcomes for pediatric patients with NHL have improved substantially, the focus has now shifted to minimizing the long-term toxicity of therapy. Novel targeted agents are desirable as they have the potential to improve outcomes and decrease the reliance on toxic conventional chemotherapy.

Bibliography is available at Expert Consult.

496.3 Late Effects in Children and Adolescents with Lymphoma
Jessica Hochberg, Lisa Giulino-Roth, and Mitchell S. Cairo

The majority of patients with newly diagnosed HL and NHL have OS rates above 90%. There are approximately 270,000 survivors of childhood cancer in the United States, which equates to about 1 of every 640 adults between the ages of 20 and 40 yr. However, this survival has often been achieved at the expense of an increased relative risk of long-term complications, including solid tumors, leukemia, cardiac disease, pulmonary complications, thyroid disease, and infertility. An analysis of more than 1,000 long-term childhood NHL survivors found increased rates of death >20 yr after treatment. A review of Surveillance, Epidemiology and End Results data over a 25 yr follow-up period demonstrates that the relative survival curves do not plateau after 10 yr following diagnosis of HL but, rather, accelerate. This finding highlights the importance of late morbidity and mortality among survivors of lymphoma. The first Childhood Cancer Survivor Study, a retrospective cohort study of 10,397 cancer survivors, shows that 62.3% of survivors report at least 1 chronic condition, with 27.5% reporting severe or life-threatening conditions. The survivor's adjusted relative risk of a severe or life-threatening chronic condition, compared with that of a sibling, was 8.2 (95% confidence interval, 6.9-9.7). When disease-specific health outcomes were looked at, both HL and NHL were found to be associated with a cumulative incidence of chronic health conditions approaching 70-80%, with severe conditions being reported in close to 50% of HL survivors (Fig. 496-6).
Bibliography
Figure 496-6 Percentage of attributable proportions of overall mortality risk in survivors of childhood cancer. (Adapted from Yeh JM, Nekhlyudov L, Goldie SJ, et al: A model-based estimate of cumulative excess mortality in survivors of childhood cancer, Ann Intern Med 152[7]:409–417, 2010.)
Primary central nervous system (CNS) tumors are a heterogeneous group of diseases that are, collectively, the second most common malignancy in childhood and adolescence. The overall mortality among this group approaches 30%. Patients with CNS tumors have the highest morbidity—primarily neurologic—of all children with malignancies. Outcomes have improved over time with innovations in neurosurgery and radiation therapy as well as the introduction of chemotherapy as a therapeutic modality. The treatment approach for these tumors is multimodal. Surgery with complete resection, if feasible, is the foundation, with radiation therapy and chemotherapy utilized according to the diagnosis, patient age, and other factors.

ETIOLOGY
The etiology of pediatric brain tumors is not well defined. A male predominance is noted in the incidence of medulloblastoma and ependymoma. Familial and hereditary syndromes associated with an increased incidence of brain tumors account for approximately 5% of cases (Table 497-1). Cranial exposure to ionizing radiation also is associated with a higher incidence of brain tumors. There are sporadic reports of brain tumors within families without evidence of a heritable syndrome. The molecular events associated with tumorigenesis of pediatric brain tumors are not known.

EPIDEMIOLOGY
Approximately 4,600 primary brain tumors are diagnosed each year in children and adolescents in the United States, with an overall annual incidence of approximately 47 cases/1 million children younger than 20 yr of age. The incidence of CNS tumors is highest in infants and children 5 yr of age or younger (approximately 52 cases/1 million children).

PATHOGENESIS
More than 100 histologic categories and subtypes of primary brain tumors are described in the World Health Organization (WHO) classification of tumors of the CNS. In children 0-14 yr of age, the most common tumors are pilocytic astrocytomas (PAs) and medulloblastoma/primitive neuroectodermal tumors (PNETs). In adolescents (15-19 yr), the most common tumors are pituitary tumors and PAs (Fig. 497-1).

The Surveillance, Epidemiology, and End Results program reported a slight predominance of infratentorial tumor location (43.2%), followed by the supratentorial region (40.9%), spinal cord (4.9%), and multiple sites (11%) (Fig. 497-2, Table 497-2). There are age-related differences in primary location of tumor. During the 1st yr of life, supratentorial tumors predominate and include, most commonly, choroid plexus complex tumors and teratomas. In children 1-10 yr of age, infratentorial tumors predominate, owing to the high incidence of juvenile PA and medulloblastoma. After 10 yr of age, supratentorial tumors again predominate, with diffuse astrocytomas most common. Tumors of the optic pathway and hypothalamic region, the brainstem, and the pineal–midbrain region are more common in children and adolescents than in adults.

CLINICAL MANIFESTATIONS
The clinical presentation of the patient with a brain tumor depends on the tumor location, the tumor type, and the age of the child. Signs and symptoms are related to obstruction of cerebrospinal fluid (CSF) drainage paths by the tumor, leading to increased intracranial pressure (ICP) or causing focal brain dysfunction. Subtle changes in personality, attention, and speech may precede these classic signs and symptoms; such changes often occur with supratentorial (cortical) lesions. In young children, the diagnosis of a brain tumor may be delayed because the symptoms are similar to those of more common illnesses, such as gastrointestinal disorders, with associated vomiting. Infants with open cranial sutures may present with signs of increased ICP, such as vomiting, lethargy, and irritability, as well as the later finding of macrocephaly. The classic triad of headache, nausea, and vomiting as well as papilledema is associated with midline or infratentorial tumors. Disorders of equilibrium, gait, and coordination occur with infratentorial tumors. Torticollis may occur in cases of cerebellar tonsill herniation. Blurred vision, diplopia, and nystagmus also are associated with infratentorial tumors. Tumors of the brainstem region may be associated with gaze palsy, multiple cranial nerve palsies, and upper motor neuron deficits (e.g., hemiparesis, hyperreflexia, clonus). Supratentorial tumors are more commonly associated with lateralized deficits such as focal motor weakness, focal sensory changes, language disorders, focal seizures, and reflex asymmetry. Infants with supratentorial tumors may present with premature hand preference. Optic pathway tumors manifest as visual and/or afferent oculomotor disturbances, such as decreased visual acuity, Marcus Gunn pupil (afferent pupillary defect), nystagmus, and/or visual field defects. Suprasellar region tumors and third ventricular region tumors may manifest initially as neuroendocrine deficits, such as subacute development of obesity, abnormal linear growth velocity, diabetes insipidus, galactorrhea, precocious puberty, delayed puberty, and hypothyroidism. In fact, signs of endocrine dysfunction preceded symptoms of neuroophthalmologic dysfunction by an average of 1.9 yr, and their recognition as a possible sign of hypothalamic or pituitary neoplasm can hasten diagnosis and improve outcome. The diencephalic syndrome, which manifests as failure to thrive, emaciation despite normal caloric intake, and inappropriate normal or happy affect, occurs in infants and young children with tumors in these regions. Parinaud syndrome is seen with pineal region tumors and is manifested by paresis of upward gaze, pupillary caliber reactive to accommodation but not to light (pseudo-Argyll Robertson pupil), nystagmus to convergence or retraction, and eyelid retraction. Spinal cord tumors and spinal cord dissemination of brain tumors may manifest as long nerve tract motor and/or sensory symptoms related to obstruction of CSF drainage.
deficits often localized to below a specific spinal level, bowel and bladder deficits, and back or radicular pain. The signs and symptoms of meningeal metastatic disease from brain tumors or leukemia include head or back pain and symptoms referable to compression of cranial nerves or spinal nerve roots.

**DIAGNOSIS**

The evaluation of a patient in whom a brain tumor is suspected is an emergency. Initial evaluation should include a complete history, physical (including ophthalmic) examination, and neurologic assessment with neuroimaging. For primary brain tumors, MRI with and without gadolinium is the neuroimaging standard. Tumors in the pituitary/suprasellar region, optic path, and infratentorium are better delineated with MRI than with CT. Patients with tumors of the midline and the pituitary/suprasellar/optic chiasmal region should undergo evaluation for **neuroendocrine dysfunction**. Formal ophthalmologic examination is beneficial in patients with optic path region tumors to document the impact of the disease on oculomotor function, visual acuity, and fields of vision. The suprasellar and pineal regions are preferential sites for germ cell tumors (Fig. 497-3). Both serum and CSF measurements of $\beta$-human chorionic gonadotropin and $\alpha$-fetoprotein can assist in the diagnosis of germ cell tumors. In tumors with a propensity for spreading to the leptomeninges, such as medulloblastoma/PNET, ependymoma, and germ cell tumors, lumbar puncture with cytologic analysis of the CSF is indicated; lumbar puncture is contraindicated in individuals with newly diagnosed hydrocephalus secondary to CSF flow obstruction, in tumors that cause supratentorial midline shift, and in individuals with infratentorial tumors. Lumbar puncture in deficits often localized to below a specific spinal level, bowel and bladder deficits, and back or radicular pain. The signs and symptoms of meningeal metastatic disease from brain tumors or leukemia include head or back pain and symptoms referable to compression of cranial nerves or spinal nerve roots.

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these individuals may lead to brain herniation, resulting in neurologic compromise and death. Therefore, in children with newly diagnosed intracranial tumors and signs of increased ICP, the lumbar puncture usually is delayed until surgery or shunt placement.

**SPECIFIC TUMORS**

**Astrocytomas**

Astrocytomas are a heterogeneous group of tumors that account for approximately 40% of pediatric CNS malignancies. These tumors occur throughout the CNS.

Low-grade astrocytomas (LGAs), the predominant group of astrocytomas in childhood, are characterized by an indolent clinical course. PA is the most common astrocytoma in children, accounting for approximately 20% of all brain tumors. On the basis of clinicopathologic features using the WHO Classification System, PA is classified as a WHO grade I tumor. Although PA can occur anywhere in the CNS, the classic site is the cerebellum (Fig. 497-4A). Other common sites include the hypothalamic/third ventricular region and the optic nerve and chiasmal region (Fig. 497-4B). The classic but not exclusive neuroradiologic finding in PA is the presence of a contrast medium–enhancing nodule within the wall of a cystic mass (Fig. 497-4A). The microscopic findings include the biphasic appearance of bundles of compact fibrillary tissue interspersed with loose microcystic, spongy areas. The presence of Rosenthal fibers, which are condensed masses of glial filaments occurring in the compact areas, helps establish the diagnosis. PA has a low metastatic potential and is rarely invasive. A

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**Figure 497-2** Childhood brain tumors occur at any location within the central nervous system. The relative frequency of brain tumor histologic types and the anatomic distribution are shown. (Redrawn from Albright AL: Pediatric brain tumors, CA Cancer J Clin 43:272–288, 1993.)

**Figure 497-3** Axillary T1-weighted MR image with gadolinium of a 10 yr old boy presenting with mixed germ cell tumor of the pineal region, with early onset of puberty, headaches, and elevated \( \alpha \)-fetoprotein and \( \beta \)-human chorionic gonadotropin in the spinal fluid and serum.

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**Table 497-2** Posterior Fossa Tumors of Childhood

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>RELATIVE INCIDENCE (%)</th>
<th>PRESENTATION</th>
<th>DIAGNOSIS</th>
<th>PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>35-40</td>
<td>2-3 mo of headaches, vomiting, truncal ataxia</td>
<td>Heterogeneously or homogeneously enhancing fourth ventricular mass; may be disseminated</td>
<td>65-85% survival; dependent on stage/type; poorer (20-70%) in infants</td>
</tr>
<tr>
<td>Cerebellar astrocytoma</td>
<td>35-40</td>
<td>3-6 mo of limb ataxia; secondary headaches, vomiting</td>
<td>Cerebellar hemisphere mass, usually with cystic and solid (mural nodule) components</td>
<td>90-100% survival in totally resected pilocytic type</td>
</tr>
<tr>
<td>Brainstem glioma</td>
<td>10-15</td>
<td>1-4 mo of double vision, unsteadiness, weakness, and cranial nerve dysfunction, including facial weakness, swallowing dysfunction, and oculomotor abnormalities</td>
<td>Diffusely expanded, minimally or partially enhancing mass in 80%; 20% more focal tectal or cervicomedullary lesion</td>
<td>&gt;90% mortality in diffuse tumors; better in localized</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>10-15</td>
<td>2-5 mo of unsteadiness, headaches, double vision, and facial asymmetry</td>
<td>Usually enhancing, fourth ventricular mass with cerebellopontine predilection</td>
<td>&gt;75% survival in totally resected lesions</td>
</tr>
<tr>
<td>Atypical teratoid/rhabdoid</td>
<td>&gt;5 (10-15% of infantile malignant tumors)</td>
<td>As in medulloblastoma, but primarily in infants; often associated facial weakness and strabismus</td>
<td>As in medulloblastoma, but often more laterally extended</td>
<td>≤20% survival in infants</td>
</tr>
</tbody>
</table>

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small proportion of these tumors can progress and develop leptomeningeal spread, particularly when they occur in the optic path region. A PA very rarely undergoes malignant transformation to a more aggressive tumor. A PA of the optic nerve and chiasmal region is a relatively common finding in patients with neurofibromatosis type 1 (15% incidence). Unlike in diffuse fibrillary astrocytomas, there are no characteristic cytogenetic abnormalities in PA. Other tumors occurring in the pediatric age group with clinicopathologic characteristics similar to those of PA include pleomorphic xanthoastrocytoma, desmoplastic cerebral astrocytoma of infancy, and subependymal giant cell astrocytoma.

The second most common astrocytoma is fibrillary infiltrating astrocytoma, which consists of a group of tumors characterized by a pattern of diffuse infiltration of tumor cells amidst normal neural tissue and potential for anaplastic progression. On the basis of their clinicopathologic characteristics, they are grouped as LGAs (WHO grade II), malignant astrocytomas (anaplastic astrocytoma; WHO grade III), and glioblastoma multiforme (WHO grade IV). Fibrillary LGA accounts for 15% of brain tumors. Histologically, these low-grade tumors demonstrate greater cellularity than normal brain parenchyma, with few mitotic figures, nuclear pleomorphism, and microcysts. The characteristic MRI finding is a lack of enhancement after contrast agent infusion. Molecular genetic abnormalities found among low-grade diffuse infiltrating astrocytomas include mutations of p53 and overexpression of platelet-derived growth factor α-chain and platelet-derived growth factor receptor-α. Evolution of fibrillary infiltrating astrocytoma into malignant astrocytoma is associated with cumulative acquisition of multiple molecular abnormalities.

Pilomyxoid astrocytoma occurs most commonly in the hypothalamic/optic chiasmic region and carries a high risk of local as well as cerebrospinal spread. This astrocytoma affects young children and infants. It is classified as a WHO grade II tumor.

The clinical management of LGAs focuses on a multimodal approach incorporating surgery as the primary treatment as well as radiation therapy and chemotherapy. With complete surgical resection the overall survival approaches 80-100%. In patients with partial resection (<80% resection), overall survival varies from 50-95%, depending on the anatomic location of the tumor. In the patient who has undergone partial tumor resection and has stable neurologic status, the current approach is to follow the patient closely by examination and imaging. With evidence of progression, a second surgical resection should be considered. In patients in whom a second procedure was less than complete or is not feasible, radiation therapy is beneficial. Radiation therapy is delivered to the tumor bed at a total cumulative dose ranging from 50-55 Gy given on a daily schedule over 6 wk. Historically, patients with deep midline tumors have been treated empirically with radiation therapy and without surgery or biopsy, with variable survival rates from 33-75%. Modern surgical techniques and innovative radiation therapy methodology, including proton-beam radiation, may have a positive impact on the survival and clinical outcome of these patients. The role of chemotherapy in the management of LGAs is evolving. Because of concerns regarding morbidity from radiation therapy in young children, several chemotherapy approaches have been evaluated, especially in children younger than 10 yr of age. Complete response to chemotherapy is uncommon; however, these approaches have yielded durable control of disease in 70-100% of patients. Patients with midline tumors in the hypothalamic/optic chiasmatic region (see Fig. 497-4B) have tended to do less well. Taken together, the chemotherapy approaches have permitted delay and, potentially, avoidance of radiation therapy. Chemotherapy agents given singly or in combination for LGA include carboplatin, vincristine, lomustine, procarbazine, temozolomide, and vinblastine. Observation is the primary approach in clinical management of selected patients with LGAs that are biologically indolent. One such group includes patients with neurofibromatosis type 1, in whom an LGA of the optic chiasm/optic pathway or brainstem may be found incidentally. Another group includes patients with midbrain astrocytoma who have resolution of clinical symptoms after ventricular shunting and do not require further intervention. Astrocytomas associated with tuberous sclerosis have responded to everolimus, a mammalian target of rapamycin inhibitor.

Malignant astrocytomas are much less common in children and adolescents than in adults, accounting for 7-10% of all childhood tumors. Among this group, anaplastic astrocytoma (WHO grade III,
and area of necrotic cyst formation often depends on the anatomic location of the tumor. MRI demonstrates a well-circumscribed tumor with variable and complex patterns of gadolinium enhancement, with or without cystic structures (Fig. 497-6). These tumors usually are noninvasive, extending into the ventricular lumen and/or displacing normal structures, sometimes leading to significant obstructive hydrocephalus. Histologic characteristics include perivascular pseudorosettes, ependymal rosettes, monomorphic nuclear morphology, and occasional nonpalisading foci of necrosis. Other histologic subtypes include anaplastic ependymoma (WHO grade III), which is much less common in childhood and is characterized by a high mitotic index and histologic features of microvascular proliferation and pseudopalisading necrosis. Myxopapillary ependymoma (WHO grade I) is a slow-growing tumor arising from the filum terminale and conus medullaris and appears to be a biologically different subtype. There are no well-defined characteristic cytogenetic or molecular genetic alterations in ependymoma, largely owing to their heterogeneous nature, although association of various genotypes with susceptibility to ependymoma have been implicated. Preliminary studies suggest that there are genetically distinct subtypes of ependymoma, exemplified by an association between alterations in the NF2 gene and spinal ependymoma. Surgery is the primary treatment modality, with extent of surgical resection a major prognostic factor. Two other major prognostic factors are age, with younger children having poorer outcomes, and tumor location, with localization in the posterior fossa, which often is seen in young children, associated with poorer outcomes. Surgery alone is rarely curative. Multimodal therapy incorporating irradiation with surgery has resulted in long-term survival in approximately 40% of patients with ependymoma undergoing gross total resection. Recurrence is predominantly local. Ependymoma is sensitive to a spectrum of chemotherapeutic agents; the role of chemotherapy in multimodal therapy of ependymoma is still unclear. Current investigations are directed toward identification of optimal radiation dose, surgical questions addressing the use of second-look procedures after chemotherapy, and further evaluation of classic as well as novel chemotherapeutic agents.

**Ependymal Tumors**

Ependymal tumors are derived from the ependymal lining of the ventricular system. Ependymoma (WHO grade II) is the most common of these neoplasms, occurring predominantly in childhood and accounting for 10% of childhood tumors. Approximately 70% of ependymomas in childhood occur in the posterior fossa. The mean age of patients is 6 yr, with approximately 40% of cases occurring in children younger than 4 yr of age. The incidence of leptomeningeal spread approaches 10% overall. Clinical presentation can be insidious and often depends on the anatomic location of the tumor. MRI demonstrates a well-circumscribed tumor with variable and complex patterns of gadolinium enhancement, with or without cystic structures (Fig. 497-6). These tumors usually are noninvasive, extending into the ventricular lumen and/or displacing normal structures, sometimes leading to significant obstructive hydrocephalus. Histologic characteristics include perivascular pseudorosettes, ependymal rosettes, monomorphic nuclear morphology, and occasional nonpalisading foci of necrosis. Other histologic subtypes include anaplastic ependymoma (WHO grade III), which is much less common in childhood and is characterized by a high mitotic index and histologic features of microvascular proliferation and pseudopalisading necrosis. Myxopapillary ependymoma (WHO grade I) is a slow-growing tumor arising from the filum terminale and conus medullaris and appears to be a biologically different subtype. There are no well-defined characteristic cytogenetic or molecular genetic alterations in ependymoma, largely owing to their heterogeneous nature, although association of various genotypes with susceptibility to ependymoma have been implicated. Preliminary studies suggest that there are genetically distinct subtypes of ependymoma, exemplified by an association between alterations in the NF2 gene and spinal ependymoma. Surgery is the primary treatment modality, with extent of surgical resection a major prognostic factor. Two other major prognostic factors are age, with younger children having poorer outcomes, and tumor location, with localization in the posterior fossa, which often is seen in young children, associated with poorer outcomes. Surgery alone is rarely curative. Multimodal therapy incorporating irradiation with surgery has resulted in long-term survival in approximately 40% of patients with ependymoma undergoing gross total resection. Recurrence is predominantly local. Ependymoma is sensitive to a spectrum of chemotherapeutic agents; the role of chemotherapy in multimodal therapy of ependymoma is still unclear. Current investigations are directed toward identification of optimal radiation dose, surgical questions addressing the use of second-look procedures after chemotherapy, and further evaluation of classic as well as novel chemotherapeutic agents.

**Choroid Plexus Tumors**

Choroid plexus tumors account for 2-4% of childhood CNS tumors. They are the most common CNS tumor in children younger than 1 yr of age and account for 10-20% of CNS tumors in infants. These tumors are intraventricular epithelial neoplasms arising from the choroid plexus. Children present with signs and symptoms of increased ICP.
Infants may present with macrocephaly and focal neurologic deficits. In children, these tumors predominantly occur supratentorially in the lateral ventricles. **Choroid plexus papilloma** (WHO grade I), the most common of this group, is a well-circumscribed lesion on neuroimaging and closely resembles normal choroid plexus histologically. **Choroid plexus carcinoma** (WHO grade III) is a malignant tumor with metastatic potential to seed into the CSF pathways. This malignancy has the following histologic characteristics: nuclear pleomorphism, high mitotic index, and increased cell density. Immunopositivity for transthyretin (prealbumin) is useful in confirming the diagnosis of choroid plexus tumors. These tumors are associated with the **Li-Fraumeni syndrome**. Simian virus 40 may also play an etiologic role in choroid plexus tumors. After complete surgical resection, the frequency of cure for choroid plexus papilloma approaches 100%, whereas the frequency of cure for choroid plexus carcinoma approaches 20-40%. Reports suggest that radiation therapy and/or chemotherapy may lead to better disease control for choroid plexus carcinoma.

**Embryonal Tumors**

Embryonal tumors or PNETs are the most common group of malignant CNS tumors of childhood, accounting for approximately 20% of pediatric CNS tumors. They have the potential to metastasize to the neuraxis and beyond. The group includes medulloblastoma, supratentorial PNET, ependymoblastoma, medulloepithelioblastoma, and atypical teratoid/rhabdoid tumor, all of which are histologically classified as WHO grade IV tumors.

**Medulloblastoma**, which accounts for 90% of embryonal CNS tumors, is a cerebellar tumor occurring predominantly in males and at a median age of 5-7 yr. Most of these tumors occur in the midline cerebellar vermis; however, older patients may present with tumors in the cerebellar hemisphere. CT and MRI demonstrate a solid, homogeneous, contrast medium–enhancing mass in the posterior fossa causing fourth ventricular obstruction and hydrocephalus (Fig. 497-7). Up to 30% of patients with medulloblastoma present with neuroimaging evidence of leptomeningeal spread. Among a variety of diverse histologic patterns of this tumor, the most common is a monomorphic sheet of undifferentiated cells classically noted as small, blue, round cells. Neuronal differentiation is more common among these tumors and is characterized histologically by the presence of Homer Wright rosettes and by immunopositivity for synaptophysin. An anaplastic variant is often more aggressive and may be associated with worse prognosis.

Patients present with signs and symptoms of increased ICP (i.e., headache, nausea, vomiting, mental status changes, and hypertension) and cerebellar dysfunction (i.e., ataxia, poor balance, dysmetria). Standard clinical staging evaluation includes MRI of the brain and spine, both preoperatively and postoperatively, as well as as lumbar puncture after the increased ICP has resolved. The Chang staging system, originally based on surgical information, has been modified to incorporate information from neuroimaging to identify risk categories. Clinical features that have consistently demonstrated prognostic significance include age at diagnosis, extent of disease, and extent of surgical resection. Patients younger than 4 yr of age have a poor outcome, partly as the result of a higher incidence of disseminated disease on presentation and past therapeutic approaches that have used less intense therapies. Patients with disseminated disease at diagnosis (M >0), including positive CSF cytologic result alone (M1), have a markedly worse outcome than those without dissemination (M0). Similarly, patients with gross residual disease after surgery have worse outcomes than those in whom surgery achieved gross total resection of disease.

Cytogenetic and molecular genetic studies have demonstrated multiple abnormalities in medulloblastoma. The most common abnormality involves chromosome 17p deletions, which occur in 30-40% of all cases. These deletions are not associated with P53 mutations. Several signaling pathways have been shown to be active in medulloblastomas, including the sonic hedgehog (SHH) pathway, predominately associated with the desmoplastic variants, and the WNT pathway, which can occur in up to 15% of cases and has been associated with improved survival. Integrative genomic studies have recently identified at least 4 distinct molecular subgroups of medulloblastoma—WNT, SHH, group 3, and group 4—which exhibit highly discriminate transcriptional, cytogenetic, and mutational spectra, in addition to divergent patient demographics and clinical behavior. These prognostic groups still must be validated in larger prospective studies. With the evolution of gene array technology, preliminary studies have identified clusters of genes/gene expression that appear to be associated with metastatic medulloblastoma and outcome.

A multimodal treatment approach is pursued in medulloblastoma, with surgery as the starting point of treatment. Medulloblastoma is sensitive to both chemotherapy and radiation therapy. With technology advances in neurosurgery, neuroradiology, and radiation therapy, as well as identification of chemotherapeutic as an effective modality, the overall outcome among all patients approaches 60-70%. Standard
Supratentorial primitive neuroectodermal tumors (SPNETs) account for 2-3% of childhood brain tumors, primarily in children within the 1st decade of life. These tumors are similar histologically to medulloblastoma and are composed of undifferentiated or poorly differentiated neuroepithelial cells. Historically, patients with SPNETs have had poorer outcomes than those with medulloblastoma after combined-modality therapy. In current clinical trials, children with SPNETs are considered among the high-risk group and receive dose-intensive chemotherapy with craniospinal radiation therapy. The characteristic cytogenetic pattern is partial or complete deletion of chromosome 22q11.2 that is associated with mutation in the INI1 gene. The relation between this mutation and tumorigenesis is unclear. Outcome after combined-modality therapy with intensive chemotherapy is very poor and there is no standard chemotherapy. However, long-term survival is reported for some children, primarily with complete resection and focal radiotherapy.

Pineal Parenchymal Tumors
The pineal parenchymal tumors are the most common malignancies after germ cell tumors that occur in the pineal region. These include pineoblastoma, occurring predominantly in childhood, pineocytoma, and the mixed pineal parenchymal tumors. The therapeutic approach in this group of diseases is multimodal. There was significant concern regarding the location of these masses and the potential complications of surgical intervention. With developments in neurosurgical technique and surgical technology, the morbidity and mortality associated with these approaches have markedly decreased. Stereotactic biopsy of these tumors may be adequate to establish diagnosis; however, consideration should be given to total resection of the lesion before institution of additional therapy. Pineoblastoma, the more malignant variant, is considered a subgroup of childhood PNETs. Chemotherapy regimens incorporate cisplatin, cyclophosphamide (Cytoxan), etoposide (VP-16), and vincristine and/or lomustine. Data have shown that survival outcome of combined chemotherapy and radiation therapy in pineal-region PNETs approaches 70% at 5 yr, similar to that noted for medulloblastoma. Pineocytoma usually is approached with surgical resection.

Craniopharyngioma
Craniopharyngioma (WHO grade 1) is a common tumor of childhood, accounting for 7-10% of all childhood tumors. The adamantinomatous variant of craniopharyngioma predominates in childhood. Children with craniopharyngioma often present with endocrinologic abnormalities such as growth failure and delayed sexual maturation. Visual changes can occur and may include decreased acuity or visual field abnormalities. These tumors are often quite large and heterogeneous, displaying both solid and cystic components, and occur within the suprasellar region. They are minimally invasive, adhere to
adjacent brain parenchyma, and engulf normal brain structures. MRI demonstrates the solid tumor with cystic structures containing fluid of intermediate density. CT may show calcifications associated with the solid and cystic wall components. Surgery is the primary treatment modality, with gross total resection curative in small lesions. Controversy exists regarding the relative roles of surgery and radiation therapy in large, complex tumors. Significant morbidity (panhypopituitarism, growth failure, visual loss) is associated with these tumors and their therapy, owing to the anatomic location. There is no role for chemotherapy in craniopharyngioma.

Germ Cell Tumors
Germ cell tumors of the CNS are a heterogeneous group of tumors that are primarily tumors of childhood, arising predominantly in midline structures of the pineal and suprasellar regions (see Fig. 497-3). They account for 3-5% of pediatric brain tumors. The peak incidence of these tumors is in children 10-12 yr of age. Overall, there is a male preponderance, although there is a female preponderance for suprasellar tumors. Germ cell tumors occur multifocally in 5-10% of cases. This group of tumors is much more prevalent in Asian populations than European populations. Delays in diagnosis can occur because these tumors have a particularly insidious course; the initial presenting symptoms may be subtle, including poor school performance and behavior problems. As in peripheral germ cell tumors, the analysis of protein markers, α-fetoprotein, and β-human chorionic gonadotropin may be useful in establishing the diagnosis and monitoring treatment response. Surgical biopsy is recommended to establish the diagnosis; however, nongerminomatous germ cell tumors may be diagnosed on the basis of protein marker elevations. Therapeutic approaches to germinomas and mixed germ cell tumors are different. The survival proportion among patients with pure germinoma exceeds 90%. The postsurgical treatment of pure germinomas is somewhat controversial in defining the relative roles of chemotherapy and radiation therapy. Clinical trials have investigated the use of chemotherapy and reduced-dose radiation after surgery in pure germinomas. The therapeutic approach to nongerminomatous germ cell tumors is more aggressive, combining more intense chemotherapy regimens with craniospinal radiation therapy. Survival rates among patients with these tumors are markedly lower than those noted in patients with germinoma, ranging from 40-70% at 5 yr. Trials have shown the benefit of the use of high doses of chemotherapy with peripheral blood stem cell rescue.

Tumors of the Brainstem
Tumors of the brainstem are a heterogeneous group of tumors that account for 10-15% of childhood primary CNS tumors. Outcome depends on tumor location, imaging characteristics, and the patient’s clinical status. Patients with these tumors may present with motor weakness, cranial nerve dysfunction, cerebellar dysfunction, and/or signs of increased ICP. On the basis of MRI evaluation and clinical findings, tumors of the brainstem can be classified into 4 types: focal (5-10% of patients); dorsally exophytic (5-10%); cervicomedullary (5-10%); and diffuse intrinsic (70-85%) (Fig. 497-8). Surgical resection is the primary treatment approach for focal and dorsally exophytic tumors and leads to a favorable outcome. Histologically, these 2 groups usually are low-grade gliomas. Cervicomedullary tumors, owing to their location, may not be amenable to surgical resection but are sensitive to radiation therapy. Diffuse intrinsic tumors, characterized by the diffuse infiltrating pontine glioma, are associated with a very poor outcome independent of histologic diagnosis. These tumors are not amenable to surgical resection. Biopsy in children in whom MRI shows a diffuse intrinsic tumor is controversial and is not recommended unless there is suspicion of another diagnosis, such as infection, vascular malformation, multiple sclerosis or other disorder of myelination, or metastatic tumor. These diagnoses are much more common in adults. The standard approach for treatment of diffuse infiltrating pontine gliomas has been radiation therapy, and median survival with this treatment is 12 mo, at best. Use of chemotherapy, including high-dose chemotherapy with peripheral blood stem cell rescue, has not yet been of survival benefit in this group of patients. Current approaches include evaluation of investigational agents alone or in combination with radiation therapy, similar to approaches being pursued in patients with malignant gliomas.

Metastatic Tumors
Metastatic spread of other childhood malignancies to the brain is uncommon. Childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma can spread to the leptomeninges, causing symptoms of communicating hydrocephalus. Chloromas, which are collections of myeloid leukemia cells, can occur throughout the neuraxis. Rarely, brain parenchymal metastases occur from lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and clear cell sarcoma of the kidney. Therapeutic approaches are based on the specific histologic diagnosis and may incorporate radiation therapy, intrathecal administration of chemotherapy, and/or systemic administration of chemotherapy. Medulloblastoma is the childhood brain tumor that most commonly metastasizes extraneurally. Less commonly, extraneural metastases from malignant glioma, PNET, and ependymoma can occur. Ventriculoperitoneal shunts have been known to allow extraneural metastases, primarily within the peritoneal cavity but also systemically.

COMPLICATIONS AND LONG-TERM MANAGEMENT
Data from the National Cancer Institute Surveillance, Epidemiology and End Results Program indicate that more than 70% of patients with childhood brain tumors will be long-term survivors. At least 50% of these survivors will experience chronic problems as a direct result of their tumors and treatment. These problems include chronic neurologic deficits such as focal motor and sensory abnormalities, seizure disorders, neurocognitive deficits (e.g., developmental delays, learning disabilities), and neuroendocrine deficiencies (e.g., hypothyroidism, growth failure, delay or absence of puberty). These patients are also at significant risk for secondary malignancies. Supportive multidisciplinary interventions for children with brain tumors both during and after therapy may help improve the ultimate outcome. Optimal seizure management, physical therapy, endocrine management with timely growth hormone and thyroid replacement therapy, tailored educational programs, and vocational interventions may enhance the childhood brain tumor survivor’s quality of life.

Bibliography is available at Expert Consult.
Bibliography


Neuroblastomas are embryonal cancers of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to very intensive multimodal therapy. The causes of most cases remain unknown, and although significant advances have been made in the treatment of children with these tumors, the outcomes for aggressive forms of neuroblastoma remain poor.

**EPIDEMIOLOGY**

Neuroblastoma is the most common extracranial solid tumor in children and the most commonly diagnosed malignancy in infants. Approximately 600 new cases are diagnosed each year in the United States, accounting for 8-10% of childhood malignancies and one third of cancers in infants. Neuroblastoma accounts for >15% of the mortality from cancer in children. The median age of children at diagnosis of neuroblastoma is 22 mo, and 90% of cases are diagnosed by 5 yr of age. The incidence is slightly higher in boys and in whites.

**PATHOLOGY**

Neuroblastoma tumors, which are derived from primordial neural crest cells, form a spectrum with variable degrees of neural differentiation, ranging from tumors with primarily undifferentiated small round cell (neuroblastoma) to tumors consisting of mature and maturing Schwannian stroma with ganglion cells (ganglioneuroblastoma or ganglioneuroma). The tumors may resemble other small round blue cell tumors, such as rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma. The prognosis of children with neuroblastoma varies with the histologic features of the tumor, and prognostic factors include the presence and amount of Schwannian stroma, the degree of tumor cell differentiation, and the mitosis-karyorrhexis index.

**PATHOGENESIS**

The etiology of neuroblastoma in most cases remains unknown. Familial neuroblastoma accounts for 1-2% of all cases, is associated with a younger age at diagnosis, and is linked to mutations in the *PHOX2B* and *ALK* genes. The *BARD1* gene has also been identified as a major genetic contributor to neuroblastoma risk. Neuroblastoma is associated with other neural crest disorders, including Hirschsprung disease, central hypoventilation syndrome, and neurofibromatosis type I, and potentially congenital cardiovascular malformations (Table 498-1). Children with Beckwith-Wiedemann syndrome and hemihypertrophy also have a higher incidence of neuroblastoma. Increased incidence of neuroblastoma is associated with some maternal and paternal occupational chemical exposures, farming, and work related to electronics, although no single environmental exposure has been shown to directly cause neuroblastoma.

Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the *MYCN* (*N-myc*) proto-oncogene and tumor cell DNA content, or ploidy (Tables 498-2 to 498-4). Amplification of *MYCN* is strongly associated with advanced tumor stage and poor outcomes. Hyperdiploidy confers better prognosis if the child is younger than 1 yr of age at diagnosis. Other chromosomal abnormalities, including loss of heterozygosity of 1p, 11q, and 14q, and gain of 17q, are commonly found in neuroblastoma tumors and are also associated with worse outcomes. In addition, many other biologic factors are associated with neuroblastoma outcomes, including tumor vascularity and the expression levels of nerve growth factor receptors (TrkA, TrkB), ferritin, lactate dehydrogenase, ganglioside GD2, neuropeptide Y, chromogranin A, CD44, multidrug resistance–associated protein, and telomerase. These factors and many others are under investigation in clinical trials to determine whether they can be used to reduce therapy for children predicted to fare well with minimal therapy and to intensify therapy for those predicted to be at high risk for relapse.

**CLINICAL MANIFESTATIONS**

Neuroblastoma may develop at any site of sympathetic nervous system tissue. Approximately half of neuroblastoma tumors arise in the adrenal glands, and most of the remainder originate in the paraspinal sympathetic ganglia. Metastatic spread, which is more common in children older than 1 yr of age at diagnosis, occurs via local invasion or distant hematogenous or lymphatic routes. The most common sites of metastasis are the regional or distant lymph nodes, long bones and skull, bone marrow, liver, and skin. Lung and brain metastases are rare, occurring in >3% of cases.

The signs and symptoms of neuroblastoma reflect the tumor site and extent of disease, and the symptoms of neuroblastoma can mimic many other disorders, a fact that can result in a delayed diagnosis. Metastatic disease can cause a variety of signs and symptoms, including fever, irritability, failure to thrive, bone pain, cytopenias, bluish subcutaneous nodules, orbital proptosis, and peri orbital ecchymoses (Fig. 498-1). Localized disease can manifest as an asymptomatic mass or can cause

<table>
<thead>
<tr>
<th>Table 498-1</th>
<th>Syndromes Associated with Neuroblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPONYM</strong></td>
<td><strong>FEATURES</strong></td>
</tr>
<tr>
<td>Pepper syndrome</td>
<td>Massive involvement of the liver with metastatic disease with or without respiratory distress.</td>
</tr>
<tr>
<td>Horner syndrome</td>
<td>Unilateral ptosis, myosis, and anhidrosis associated with a thoracic or cervical primary tumor. Symptoms do not resolve with tumor resection.</td>
</tr>
<tr>
<td>Hutchinson syndrome</td>
<td>Limping and irritability in young child associated with bone and bone marrow metastases.</td>
</tr>
<tr>
<td>Opsoclonus-myoclonus-ataxia syndrome</td>
<td>Myoclonic jerking and random conjugate eye movements with or without cerebellar ataxia. Often associated with a biologically favorable and differentiated tumor. The condition is likely immune mediated, may not resolve with tumor removal, and often exhibits progressive neuropsychologic sequelae.</td>
</tr>
<tr>
<td>Kerner-Morrison syndrome</td>
<td>Intractable secretory diarrhea due to tumor secretion of vasointestinal peptides. Tumors are generally biologically favorable.</td>
</tr>
<tr>
<td>Neurocristopathy syndrome</td>
<td>Neuroblastoma associated with other neural crest disorders, including congenital hypoventilation syndrome or Hirschsprung disease. Germline mutations in the paired homeobox gene <em>PHOX2B</em> have been identified in a subset of patients with this disease.</td>
</tr>
<tr>
<td>ROHHAD</td>
<td>Approximately 40% may have neural crest-derived tumors. Obesity and neurologic issues may be part of a paraneoplastic syndrome.</td>
</tr>
</tbody>
</table>

ROHHAD, rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation.

symptoms because of the mass itself, including spinal cord compression, bowel obstruction, and superior vena cava syndrome. Children with neuroblastoma can also present with neurologic signs and symptoms. Neuroblastoma originating in the superior cervical ganglion can result in Horner syndrome. Paraspinal neuroblastoma tumors can invade the neural foramina, causing spinal cord and nerve root compression. Neuroblastoma can also be associated with a paraneoplastic syndrome of autoimmune origin, termed opsoclonus–myoclonus–ataxia syndrome, in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination,
and cognitive dysfunction. Some tumors produce catecholamines that can cause increased sweating and hypertension, and some release vasoactive intestinal peptide, causing a profound secretory diarrhea. Children with extensive tumors can also experience tumor lysis syndrome and disseminated intravascular coagulation. Infants younger than 1 yr of age also can present in unique fashion, termed stage 4S, with widespread subcutaneous tumor nodules, massive liver involvement, limited bone marrow disease, and a small primary tumor without bone involvement or other metastases.

**DIAGNOSIS**

Neuroblastoma is usually discovered as a mass or multiple masses on plain radiography, CT, or MRI (Fig. 498-2A). The mass often contains calcification and hemorrhage that can be appreciated on plain radiography or CT. Prenatal diagnosis of neuroblastoma on maternal ultrasound scans is sometimes possible. Tumor markers, including catecholamine metabolites homovanillic acid and vanillylmandelic acid, are elevated in the urine of approximately 95% of cases and help to confirm the diagnosis. A pathologic diagnosis is established from tumor tissue obtained by biopsy. Neuroblastoma can be diagnosed without a primary tumor biopsy if small round blue tumor cells are observed in bone marrow samples (Fig. 498-3) and the levels of vanillylmandelic acid or homovanillic acid are elevated in the urine.

Evaluations for metastatic disease should include CT or MRI of the chest and abdomen, bone scans to detect cortical bone involvement, and at least 2 independent bone marrow aspirations and biopsies to evaluate for marrow disease. Iodine-123 metaiodobenzylguanidine (123I-MIBG) studies should be used when available to better define the extent of disease (see Fig. 498-2B and C). MRI of the spine should be performed in cases with suspected or potential spinal cord compression, but imaging of the brain with either CT or MRI is not routinely performed unless dictated by the clinical presentation.

The **International Neuroblastoma Staging System (INSS)** is currently used to stage patients with neuroblastoma after initial surgical resection (see Table 498-3). INSS stage 1 tumors are confined to the organ or structure of origin and are completely resected. INSS stage 2 tumors extend beyond the structure of origin but not across the midline, either with (stage 2B) or without (stage 2A) ipsilateral lymph node involvement. INSS stage 3 tumors extend beyond the midline, with or without bilateral lymph node involvement, whereas INSS stage 4 tumors are disseminated, with metastases to bones, bone marrow, liver, distant lymph nodes, and other organs. INSS stage 4S refers to neuroblastoma in children younger than 1 yr of age with dissemination to liver, skin, and/or bone marrow without bone involvement and with a primary tumor that would otherwise be staged as INSS stage 1 or 2. A new International Neuroblastoma Risk Group Staging System was recently developed to allow for more effective comparisons of treatments and outcomes worldwide.

**TREATMENT**

Treatment strategies for neuroblastoma have changed dramatically over the past 20 yr, with significant reduction in treatment intensity for children who have localized low-risk tumors and with continued increased treatment intensity and addition of new agents for treatment of children who have high-risk neuroblastoma. The patient’s age and tumor stage are combined with cytogenetic and molecular features of the tumor to determine the treatment risk group and estimated prognosis for each patient (see Tables 498-2 to 498-4). The usual treatment for children with low-risk neuroblastoma is surgery for stages 1 and 2 and observation for stage 4S with cure rates generally >90% without further therapy. Treatment with chemotherapy or radiation for the rare child with local recurrence can still be curative. Children with spinal cord compression at diagnosis also may require urgent treatment with chemotherapy, surgery, or radiation to avoid neurologic

| **Table 498-4** Phenotypic and Genetic Features of Neuroblastoma, Treatment, and Survival According to Prognostic Category |
|---------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| **VARIABLE**                     | **PROGNOSTIC CATEGORY**       | **Tumor Stage 4S**            |
| **VARIABLE**                     | **Low Risk**                  | **Intermediate Risk**         | **High Risk**                 | **Tumor Stage 4S**            |
| Pattern of disease              | Localized tumor               | Localized tumor with          | Metastases to bone marrow and | Metastases to liver and      |
|                                 |                               | locoregional lymph node       | bone (except in infants)      | skin (with minimal bone      |
|                                 |                               | extension; metastases to bone |                               | marrow involvement) in       |
|                                 |                               | marrow and bone in infants    |                               | infants                      |
| Tumor genomics                  | Whole-chromosome gains        | Whole-chromosome gains        | Segmental chromosomal         | Whole-chromosome gains       |
|                                 |                               |                               | aberrations                   |                               |
| Treatment                       | Surgery                       | Moderate-intensity            | Dose-intensive chemotherapy,  | Supportive care              |
|                                 |                               | chemotherapy; surgery         | surgery, and external-beam    |                               |
|                                 |                               |                               | radiotherapy to primary tumor |                               |
|                                 |                               |                               | and resistant metastatic      |                               |
|                                 |                               |                               | sites; myeloablative          |                               |
|                                 |                               |                               | chemotherapy with             |                               |
|                                 |                               |                               | autologous hematopoietic stem |                               |
|                                 |                               |                               | cell rescue; isotretinoin with |                               |
|                                 |                               |                               | anti–ganglioside GD2          |                               |
|                                 |                               |                               | immunotherapy                 |                               |
| Survival rate                   | >98%                          | 90-95%                        | 40-50%                        | >90%                         |

* Patients are assigned to prognostic groups according to risk, as described by the Children’s Oncology Group, with the level of risk defining the likelihood of death from disease. Stage 4S disease is considered separately here because of the unique phenotype of favorable biologic features and relentless early progression but ultimately full and complete regression of the disease.

† The goal of surgery is to safely debulk the tumor mass and avoid damage to surrounding normal structures while also obtaining sufficient material for molecular diagnostic studies. Some localized tumors may spontaneously regress without surgery.

‡ Low-dose chemotherapy or radiation therapy, or both, is used in patients with life-threatening hepatic involvement, especially in infants <2 mo of age, who are at much higher risk for life-threatening complications from massive hepatomegaly. From Maris JM: Recent advances in neuroblastoma, N Engl J Med 362:2202–2210, 2010.
noin, Accutane). Induction chemotherapy for children with high-risk neuroblastoma includes combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. After completion of induction chemotherapy, resection of the residual primary tumor is followed by high-dose chemotherapy with autologous stem cell rescue and focal radiation therapy to tumor sites. A national cooperative group trial demonstrated significantly better survival with chemotherapy plus autologous stem cell rescue than with chemotherapy alone. The further addition of 13-cis-retinoic acid after autologous stem cell transplantation resulted in further improvements in survival rates. In addition, a national clinical trial has demonstrated an increase in short-term survival rates with the addition of the monoclonal antibody ch14.18, interleukin 2, and granulocyte-macrophage colony-stimulating factor to 13-cis-retinoic acid therapy.

Cases of high-risk neuroblastoma are associated with frequent relapses, and children with recurrent neuroblastoma have a <50% response rate to alternative chemotherapy regimens. New treatment strategies and agents are needed for children with both high-risk and recurrent neuroblastoma. Therapies currently under investigation include new chemotherapeutic agents and other novel therapies directed against critical intracellular signaling pathways, radiolabeled targeted agents (such as 131I-MIBG), immunotherapy, and antitumor vaccines. Ongoing biologic studies of neuroblastoma will also hopefully lead to the identification of new molecular and genetic targets for therapy.

Bibliography is available at Expert Consult.

damage. Stage 4S neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy. Chemotherapy or resection of the primary tumor does not improve survival rates, but for infants with massive liver involvement and respiratory compromise, small doses of cyclophosphamide or low-dose hepatic irradiation may alleviate symptoms. For children with stage 4S neuroblastoma who require treatment for symptoms, the survival rate is 81%.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and, in some cases, radiation therapy. The chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide, and doxorubicin given for several months. Radiation therapy is used for tumors with incomplete response to chemotherapy. Children with intermediate-risk neuroblastoma, including children with stage 3 disease and infants with stage 4 disease and favorable characteristics, have an excellent prognosis and >90% survival with this moderate treatment. In this intermediate-risk group, obtaining adequate diagnostic material for determination of the underlying biologic features of the tumor, such as the Shimada pathologic classification and MYCN gene amplification, is critical, so that children with unfavorable characteristics can receive more-aggressive treatment and those with favorable features can be spared excessive toxic therapy.

Children with high-risk neuroblastoma have long-term survival rates between 25% and 35% with current treatment that consists of intensive chemotherapy, high-dose chemotherapy with autologous stem cell rescue, surgery, radiation, and 13-cis-retinoic acid (isotreti-
Bibliography


Wilms tumor (WT), also known as nephroblastoma, is the most common primary malignant renal tumor of childhood; other renal tumors are very rare. It is the second most common malignant
abdominal tumor in childhood. The most common sites of metastases are the lungs, regional lymph nodes, and liver. Histologically, the classic WT is made up of varying proportions of blastemal, stromal, and epithelial cells, recapitulating stages of normal renal development. The treatment includes surgery and chemotherapy with or without radiotherapy. The use of multimodality treatment and multiinstitutional cooperative group trials has dramatically improved the cure rate of WT from <30% to approximately 90% (Table 499-1).

**Epidemiology**

WT accounts for 6% of pediatric malignancies and more than 95% of kidney tumors in children. In the United States, the incidence of WT is approximately 8 cases per 1 million children younger than 15 yr of age per year, and about 650 new cases are diagnosed each year. Approximately 75% of the cases occur in children younger than 5 yr with a peak incidence at 2-3 yr of age. It can arise in 1 or both kidneys; the incidence of bilateral WTs is 7%. Most cases are sporadic, but approximately 2% of patients have a family history. In 8-10% of patients, WT is observed in the context of hemihypertrophy, aniridia, genitourinary abnormalities, and a variety of rare syndromes, including Beckwith-Wiedemann syndrome and Denys-Drash syndrome (Table 499-2). An earlier age of diagnosis and an increased incidence of bilateral disease are generally observed in syndromic and familial cases.

### Table 499-1

<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>STAGE</th>
<th>RECURRENCE-FREE SURVIVAL (%)</th>
<th>OVERALL SURVIVAL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>I</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>Favorable</td>
<td>II</td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>Favorable</td>
<td>III</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>Favorable</td>
<td>IV</td>
<td>75</td>
<td>81</td>
</tr>
<tr>
<td>Favorable</td>
<td>V</td>
<td>65</td>
<td>78</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>I</td>
<td>69</td>
<td>82</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>II-III</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>IV</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

### Table 499-2

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>CLINICAL CHARACTERISTICS</th>
<th>GENETIC ANOMALIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation (WAGR)</td>
<td>Aniridia, genitourinary abnormalities, mental retardation</td>
<td>Del 11p13 (WT1 and PAX6)</td>
</tr>
<tr>
<td>Denys-Drash</td>
<td>Early-onset renal failure with renal mesangial sclerosis, male pseudohermaphroditism</td>
<td>WT1 missense mutation</td>
</tr>
<tr>
<td>Beckwith-Wiedemann</td>
<td>Organomegaly (liver, kidney, adrenal, pancreas) macroglossia, omphalocele, hemihypertrophy</td>
<td>Unilateral paternal disomy, duplication of 11p15.5, loss of imprinting, mutation of p57KIP57</td>
</tr>
</tbody>
</table>

**Etiology: Genetics and Molecular Biology**

WT is thought to be derived from incompletely differentiated renal mesenchyme, and tumors are typically composed of cells reminiscent of the undifferentiated and partially differentiated cells that normally arise from renal mesenchyme. Foci of benign, undifferentiated mesenchyme (nephrogenic rests) that persist abnormally in the kidney into postnatal life are observed in approximately 1% of children in the general population, but are present in up to 90% of children who have a family history of WT, develop bilateral tumors, or display features of WT-related syndromes. Nephrogenic rests usually regress or differentiate, but those that persist can become malignant.

To date genetic mutations have been detected, either individually or in combination, in a third of WTs. Mutations in WT1, a gene located at 11p13 and encoding a zinc finger transcription factor, are observed in 15-20% of tumors. These are homozygous and result in loss of WT1 function. The majority of WT1 mutations are somatic, result in loss of WT1 function, and are present homozygously. However, germline WT1 mutations are also observed, primarily in patients with WT-associated syndromes, or sometimes in patients with bilateral disease. In these instances, the wild-type allele present in the germline is mutated or lost in the tumor, resulting in loss of WT1 function. Interestingly, nephrogenic rests assessed from patients heterozygous for a germline WT1 mutation are homozygous for the WT1 mutation, with additional somatic mutations being observed in the autologous tumors. The vast majority of WT1 mutations are deletion/truncating mutations or missense mutations that affect amino acid residues critical for WT1 function. Germline truncating mutations are usually associated with WT in the context of genitourinary anomalies or the WAGR (Wilms, aniridia, genitourinary anomalies, mental retardation) syndrome. Missense germline mutations are usually observed in children with Denys-Drash syndrome in which early-onset renal failure is observed.

Mutations in CTNNB1, encoding β-catenin, which acts as a major regulatory point in the wnt signaling pathway and also acts at the cytoplasmic membrane, are observed in approximately 15% of WTs, very often those that have sustained WT1 mutations. WTX, a gene located on the X chromosome that encodes a protein that also plays a role in wnt pathway regulation, is mutated in approximately 20% of tumors. CTNNB1 and WTX mutations are somatic. Somatic mutation of the p53 gene, TP53, is observed in approximately 5% of tumors and is associated with anaplastic tumor histology, a poor prognostic feature of WT.

In approximately 70% of tumors, loss of heterozygosity (usually copy number neutral) or loss of imprinting at imprinted loci at 11p15 is observed. This epigenetic alteration (the observation of which led to the designation of a “WT2” gene) occurs in tumors both with and without WT1, CTNNB1, or WTX mutations, and often results in biallelic expression of IGF2, a normally imprinted gene that encodes insulin-like growth factor 2, in addition to the loss of imprinting of other 11p15 genes. Families with Beckwith-Wiedemann syndrome, a somatic overgrowth syndrome in which predisposition to embryonal tumors (including WT) is observed, have been genetically linked to 11p15, and microdeletions within the IGF2 imprinting control region are present in Beckwith-Wiedemann syndrome families in which WT is observed.

WT is occasionally observed in families with a predisposition to pleuropulmonary blastoma, and mutations in the DICER1 gene, located at 14q31 and encoding a key protein in the generation of microRNAs, are observed in these families. However, outside the context of these families, DICER1 mutations are rare in WTs.

A family history of WT is noted in approximately 2% of WT patients, and predisposition is inherited as an autosomal dominant trait with incomplete penetrance. Predisposition to other tumor types or other phenotypes are not observed in the vast majority of these families. WT1 mutations are detected in <3% of families, and these WT1-related families are small, with only 2 affected individuals. Genetic linkage analyses of large WT families have localized predisposition genes to 19q and 17q, but neither gene has been identified yet. However, some
families carry neither of these mutations, suggesting that additional WT loci exist. Some families are not linked to either of these genomic regions, indicating that additional WT predisposition genes exist. Similarly, somatic alterations at 1q, 7p, 16q, chromosome 12, and other genomic regions are observed in some WT and are thought to harbor genes important in WT development.

**CLINICAL PRESENTATION**

The most common initial clinical presentation for WT is the incidental discovery of an asymptomatic abdominal mass by parents while bathing or clothing an affected child or by a physician during a routine physical examination (Table 499-3). At presentation the mass can be quite large because retroperitoneal masses can grow unhampered by strict anatomic boundaries. Functional defects in paired organs like the kidney, with good functional reserve, are also unlikely to be detected early. Hypertension is present in approximately 25% of tumors at presentation and has been attributed to increased renin activity. Abdominal pain, gross painless hematuria, and fever are other frequent findings at diagnosis. Occasionally, rapid abdominal enlargement and anemia occur as a result of bleeding into the renal parenchyma or pelvis. WT thrombus extends into the inferior vena cava in 4-10% of patients, and rarely into the right atrium. Patients might also have microcytic anemia from iron deficiency or anemia of chronic disease, polycythemia, elevated platelet count, and acquired deficiency of von Willebrand factor or factor VII deficiency.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

An abdominal mass in a child should be considered malignant until diagnostic imaging, laboratory findings, and pathology can define its true nature (see Table 499-3). Imaging studies include plain abdominal radiography, abdominal ultrasonography, and CT of the abdomen to define the intrarenal origin of the mass and differentiate it from adrenal masses (e.g., neuroblastoma) and other masses in the abdomen. Abdominal ultrasonography helps differentiate solid from cystic masses. WT might show focal areas of necrosis or hemorrhage and hydrenephrosis caused by obstruction of the renal pelvis by the tumor. Ultrasonography with Doppler imaging of renal veins and the inferior vena cava is useful to define the extent of the disease, integrity of the contralateral kidney, and metastasis. MRI requires sedation in young children and is not routinely used; it may be helpful in defining an extensive tumor thrombus that extends up to the level of the hepatic veins or even into the right atrium, and to distinguish WT from nephrogenic rests. Chest CT is more sensitive than chest radiography to screen for pulmonary metastasis, and is preferably performed before surgery because effusions and atelectasis can confound the interpretation of postoperative imaging studies. A bone scan is performed if the histologic diagnosis confirms clear cell sarcoma of the kidney to look for bone metastasis. Brain imaging with CT or MRI is obtained in cases of clear cell sarcoma of the kidney or rhabdoid tumor of the kidney as these tumors can spread to the brain.

WT lesions are metabolically active and concentrate fluorodeoxyglucose. Regional spread and metastatic lesions can be visualized on positron emission tomography/CT scanning. The diagnosis is usually made by imaging studies and confirmed by histology at the time of nephrectomy. Although biopsy is a reliable diagnostic tool, it is discouraged as it results in disease upstaging. A core needle biopsy obtained via a posterior approach should be performed in cases of unusual presentation (older age, signs of infection, inflammation) or unusual imaging findings (significant adenopathy, no renal parenchyma seen, intratumoral calcification).

**TREATMENT**

There are 2 major schools of thought in the management of WT. The Children’s Oncology Group, formerly National Wilms Tumor Study Group, advocates upfront surgery prior to initiating treatment. On the
other hand, the International Society of Pediatric Oncology recommends preoperative chemotherapy. Each approach has advantages and limitations but they have similar outcomes. Early surgery provides accurate diagnosis and staging, and can facilitate risk-adapted therapy. Preoperative chemotherapy can make surgery easier and reduces the risk of intraoperative tumor rupture and hemorrhage. Surgery entails a radical nephrectomy with meticulous dissection to avoid rupture of the tumor capsule and lymph node sampling despite the absence of abnormal nodes on preoperative imaging studies or intraoperative assessment. Partial nephrectomy is performed in patients with bilateral disease or with unilateral WT and a predisposing syndrome such as Denys-Drash and WAGR, so as to minimize the risk of future renal failure.

Prognostic factors for risk-adapted therapy include age, stage, tumor weight, and loss of heterozygosity at chromosomes 1p and 16q (Table 499-4). Histology plays a major role in risk stratification of WT. Absence of anaplasia is considered a favorable histologic finding. Presence of anaplasia is further classified as focal or diffuse, both of which are unfavorable histologic findings.

The Children's Oncology Group has specific drug dose and schedule recommendations for risk-adapted treatment of WT. Patients with favorable histologic findings of WT have a good outcome and are generally treated in the outpatient setting. Nephrectomy alone may be sufficient for patients younger than 2 yr of age with stage I disease and a tumor weighing <550 g. Patients with stages I and II disease receive chemotherapy with 2 drugs, vincristine and actinomycin D (also called daunomycin), every 1-3 wk for a total of 18 wk (regimen EE4A). Patients with stage III or IV disease receive chemotherapy with 3 drugs (vincristine, doxorubicin, and actinomycin D) every 1-3 wk for a total of 24 wk (regimen DD4A) and radiation therapy. Patients with regional lymph node metastases, residual disease after surgery, or tumor rupture receive radiation therapy to the flank or abdomen, and those with lung metastases receive radiation therapy to the lungs. The presence of loss of heterozygosity at 1p and 16q confers an adverse prognosis, and mesenchymal cell with neural markers. Bone is the most common site of distant metastasis followed by lung, abdomen, retroperitoneum, brain, and liver. Therefore, the staging work-up should include a bone scan. Early-stage disease has an excellent prognosis, especially with the addition of doxorubicin.

**RHABDOID TUMOR OF THE KIDNEY**
Malignant rhabdoid tumor of the kidney has rhabdomyoblast-like morphology. It is a rare but aggressive cancer. Hematuria is a common presenting feature. Both rhabdoid tumor of the kidney and central nervous system atypical teratoid rhabdoid tumors have deletions and mutations of the hSNF5/INI1 gene and are considered to be related. Prognosis is poor with current therapeutic protocols. The 5 yr overall survival rate is <30%.
RENAL CELL CARCINOMA
Renal cell carcinoma (RCC) is rare in children, accounting for <5% of all renal tumors of childhood. Patients may present with frank hematuria, flank pain, and/or a palpable mass, although RCC can be asymptomatic and detected incidentally. It has a propensity to metastasize to the lungs, bone, liver, and brain. RCC can be associated with von Hippel–Lindau disease. Unlike the case for adult RCC, local lymph node involvement is not a poor prognostic indicator in pediatric RCC. Nephrectomy alone may be adequate for early-stage RCC.

Bibliography is available at Expert Consult.
Bibliography
Cancer Staging System for Rhabdomyosarcoma

T1, confined to anatomic site of origin; T2, extension and/or fixation to surrounding tissue.

Studies using antibodies to skeletal muscle (desmin, muscle-specific actin, myogenin) and reverse transcription polymerase chain reaction or, in the case of alveolar tumors, fluorescent in situ hybridization for PAX-FOX01 transcript.

Determination of the specific histologic subtype is important in treatment planning and assessment of prognosis. There are 3 recognized histologic subtypes. The embryonal type accounts for approximately 60% of all cases and has an intermediate prognosis. The botryoid type, a variant of the embryonal form in which tumor cells and an edematous stroma project into a body cavity like a bunch of grapes, is found most often in the vagina, uterus, rectum, nasopharynx, and middle ear. The alveolar type accounts for approximately 25-40% of cases and is characterized by the presence of PAX-FOXO1 fusion transcript. The tumor cells tend to grow in nests that often have cleft-like spaces resembling alveoli. Alveolar tumors occur most often in the trunk and extremities and carry the poorest prognosis. The pleomorphic type (adult form) is rare in childhood, accounting for <1% of cases.

Clinical Manifestations

The most common presenting feature of rhabdomyosarcoma is a mass that may or may not be painful. Symptoms are caused by displacement or obstruction of normal structures (Table 500-1). Origin in the nasopharynx may be associated with nasal congestion, mouth breathing, epistaxis, and difficulty with swallowing and chewing. Regional extension into the cranium can produce cranial nerve paralysis, blindness, and signs of increased intracranial pressure with headache and vomiting. When the tumor develops in the face or cheek, there may be swelling, pain, trismus, and, as extension occurs, paralysis of cranial nerves. Tumors in the neck can produce progressive swelling with neurologic symptoms after regional extension. Orbital primary tumors are usually diagnosed early in their course because of associated proptosis, periorbital edema, ptosis, change in visual acuity, and local pain. When the tumor arises in the middle ear, the most common early signs are pain, hearing loss, chronic otorrhea, or a mass in the ear canal; extensions of tumor produce cranial nerve paralysis and signs of an intracranial mass on the involved side. An unremitting croupy cough and progressive stridor can accompany rhabdomyosarcoma of the larynx. Because most of these signs and symptoms also are associated with common childhood conditions, clinicians must be alert to the possibility of tumor.

Rhabdomyosarcoma of the trunk or extremities often is first noticed after trauma and initially may be regarded as a hematoma. If the swelling does not resolve or increases, malignancy should be suspected. Involvement of the genitourinary tract can produce hematuria, obstruction of the lower urinary tract, recurrent urinary tract infections, incontinence, or a mass detectable on abdominal or rectal examination. Paratesticular tumors usually manifest as a painless, rapidly growing mass in the scrotum. Vaginal rhabdomyosarcoma may manifest as a grape-like mass of tumor tissue bulging through the vaginal orifice, known as sarcoma botryoides, and can cause urinary tract or large bowel symptoms. Vaginal bleeding or obstruction of the urethra or rectum may occur. Similar findings can be noted with uterine primaries.

### Table 500-1 Staging System for Rhabdomyosarcoma

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SITE</th>
<th>T STAGE</th>
<th>SIZE</th>
<th>NODE STATUS</th>
<th>METASTASIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FAVORABLE</td>
<td>T1 or T2</td>
<td>a or b</td>
<td>N0 or N1 or Nx</td>
<td>M0</td>
</tr>
<tr>
<td>2</td>
<td>UNFAVORABLE</td>
<td>T1 or T2</td>
<td>a</td>
<td>N0 or Nx</td>
<td>M0</td>
</tr>
<tr>
<td>3</td>
<td>UNFAVORABLE</td>
<td>T1 or T2</td>
<td>a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>4</td>
<td>ANY</td>
<td>T1 or T2</td>
<td>a or b</td>
<td>N0 or N1 or Nx</td>
<td>M1</td>
</tr>
</tbody>
</table>

T1, confined to anatomic site of origin; T2, extension and/or fixation to surrounding tissue.

Size: a, <3 cm in diameter; b, ≥5 cm in diameter.

Nodes: N0, regional nodes not involved; N1, regional nodes involved; Nx, regional node status unknown.

Metastases: M0, no distant metastases; M1, metastases present (includes positive cytology in CSF, pleural, or peritoneal fluid).
Tumors in any location may disseminate early and cause symptoms of pain or respiratory distress associated with pulmonary metastases. Extensive bone involvement can produce symptomatic hypercalcemia. In such cases, it may be difficult to identify the primary lesion.

**Diagnosis**

Early diagnosis of rhabdomyosarcoma requires a high index of suspicion. The microscopic appearance is that of a small, round, blue cell tumor. Neuroblastoma, lymphoma, and Ewing sarcoma also are small, round, blue cell tumors from which suspected rhabdomyosarcomas must be differentiated. The differential diagnosis depends on the site of presentation. Definitive diagnosis is established by biopsy, microscopic appearance, and results of immunohistochemical stains and analysis of PAX/FOXO1 expression. A lesion in an extremity may be thought to be a hematoma or hemangioma; an orbital lesion resulting in proptosis may be treated as an orbital cellulitis; or bladder-obstructive symptoms may be missed. Adolescents may ignore or be embarrassed to mention paratesticular lesions for a long time. Unfortunately, several months often elapse between the initial symptoms and biopsy. Diagnostic procedures are determined mainly by the area of involvement. CT or MRI is necessary for evaluation of the primary tumor site. With signs and symptoms in the head and neck area, radiographs should be examined for evidence of a tumor mass and for indications of bony erosion. MRI should be performed to identify intracranial extension or meningeal involvement and also to reveal bony involvement or erosion at the base of the skull. For abdominal and pelvic tumors, CT with a contrast agent or MRI can help delineate the tumor (Fig. 500-1). A radionuclide bone scan, chest CT, and bilateral bone marrow aspiration and biopsy should be performed to evaluate the patient for the presence of metastatic disease and to plan treatment. Fluorodeoxyglucose positron emission tomography is being used more frequently to enhance staging. The most critical element of the diagnostic work-up is examination of tumor tissue, which includes the use of special histochemical stains and immunostains. Molecular genetics is important to detect fusion transcripts present in alveolar rhabdomyosarcoma (PAX-FOX1). Lymph nodes also should be sampled for the presence of disease spread, especially in tumors of the extremities and in boys older than 10 yr of age with paratesticular tumors.

**Treatment**

Treatment is multidisciplinary and includes the pediatric oncologist, pediatric surgeon or other surgical subspecialist, and most often radiation oncologist. Only if the tumor is able to be completely resected, with negative margins, without loss of function or major cosmetic deformity should this be attempted initially. Unfortunately, most rhabdomyosarcomas are not completely resectable at initial diagnosis. Treatment is based on risk classification of the tumor, which is determined by the stage of tumor, the tumor histology, and the amount of tumor that was surgically resected prior to chemotherapy (“surgical group”). Stage is dependent on primary site (favorable vs unfavorable), tumor invasiveness (T1 or T2), lymph node status, tumor size, and presence of metastasis. Favorable sites include female genital, paratesticular, and head and neck (nonparameningeal) regions; all other sites are considered unfavorable. Table 500-1 shows the Children’s Oncology Group staging system for rhabdomyosarcoma.

Patients should be offered enrollment in clinical trials. Table 500-2 shows current risk stratification and outcome based on results of recent studies. Patients with low-risk disease can be cured with minimal therapy consisting of vincristine and of actinomycin with or without lower doses of cyclophosphamide; radiation therapy can be used in the case of residual disease after initial surgery. Treatment for patients with intermediate-risk disease consists of vincristine, actinomycin, and cyclophosphamide along with radiation. Clinical trials in North
The nonrhabdomyosarcoma soft tissue sarcomas constitute a heterogeneity from cyclophosphamide, late effects in the radiation field such as infertility, and exposure to vinyl chloride in adults. Survival rate is poor (12% at 5 yr) despite some responses to chemotherapy/radiation therapy.

Can occur in soft tissue, liver, and lung. Localized lesions have a favorable outcome; lesions in lung and liver often are multifocal and have a poor prognosis.

Also known as the malignant peripheral nerve sheath tumor. Develops in up to 16% of patients with neurofibromatosis type 1 (NF1); almost 50% occur in patients with NF1. Deletions of chromosome 22q11–q13 or 17q11 and p53 mutations have been reported. Commonly arises in trunk and extremities and is usually locally invasive. Complete surgical excision is necessary for survival; response to chemotherapy is suboptimal.

The most common nonrhabdomyosarcoma soft tissue sarcoma in some series. Often manifesting in the 3rd decade, but 33% of patients are younger than age 20 yr. Typically arises around the knee or thigh and is characterized by a nonrandom translocation t(X;18)(p11;q11). Wide surgical excision is necessary. Radiation therapy is effective in microscopic residual disease, and ifosfamide-based therapy is active in advanced disease.

Slow-growing tumor; tends to recur or to metastasize to lung and brain years after diagnosis. Often arises in the extremities and head and neck.

Often arises in the gastrointestinal tract and may be associated with a t(12;14)(q14;q23) translocation. Associated with Epstein-Barr virus in immunodeficiency syndromes (including AIDS). Complete surgical excision is the treatment of choice.

Fibrous soft tissue sarcoma

Adipose Liposarcoma

Fibrous Fibrosarcoma

Malignant fibrous histiocytoma

Vascular Hemangiopericytoma

Angiosarcoma

Hemangioendothelioma

Peripheral nerves Neurofibrosarcoma

Synovium Synovial sarcoma

Unknown Alveolar soft part sarcoma

Smooth muscle Leiomyosarcoma

<table>
<thead>
<tr>
<th>TISSUE TYPE</th>
<th>TUMOR</th>
<th>NATURAL HISTORY AND BIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>Liposarcoma</td>
<td>A very rare tumor. Usually arises in the extremities or retroperitoneum; associated with a nonrandom translocation, t(12;16)(q13;p11). Tends to be locally invasive and rarely metastasizes; wide local excision is the treatment of choice. The role of radiation therapy and chemotherapy in treating gross residual or metastatic disease is not established.</td>
</tr>
<tr>
<td>Fibrous</td>
<td>Fibrosarcoma</td>
<td>Most common soft tissue sarcoma in children younger than 1 yr. Congenital fibrosarcoma is a low-grade malignancy that commonly arises in the extremities or trunk and rarely metastasizes. Surgical excision is treatment of choice; dramatic responses to preoperative chemotherapy may occur. In children older than 4 yr, the natural history is similar to that in adults (a 5 yr survival rate of 60%); wide surgical excision and preoperative chemotherapy are commonly used. Associated with t(12;15)(p13;q25) or trisomy 11, also +8, +17, +20.</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>Most commonly arises in the trunk and extremities, deep in the subcutaneous layer. Histologically subdivided into storiform, giant cell, myxoid, and angiomatoid variants. The angiomatoid type tends to affect younger patients and is curable with surgical resection alone. Wide surgical excision is the treatment of choice. Chemotherapy has produced objective tumor regressions.</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>Hemangiopericytoma</td>
<td>Often arises in the lower extremities or retroperitoneum; may manifest as hypoglycemia and hypophosphatemic rickets. Both benign and malignant histology. Nonrandom translocations t(12;19)(q13;q13) and t(13;22)(q22;q13.3) have been described. Complete surgical excision is the treatment of choice. Chemotherapy and radiation therapy may produce responses.</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Rare in children; 33% arise in skin, 25% in soft tissue, and 25% in liver, breast, or bone. Associated with chronic lymphedema and exposure to vinyl chloride in adults. Survival rate is poor (12% at 5 yr) despite some responses to chemotherapy/radiation therapy.</td>
<td></td>
</tr>
<tr>
<td>Hemangioendothelioma</td>
<td>Can occur in soft tissue, liver, and lung. Localized lesions have a favorable outcome; lesions in lung and liver often are multifocal and have a poor prognosis.</td>
<td></td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>Neurofibrosarcoma</td>
<td>Also known as the malignant peripheral nerve sheath tumor. Develops in up to 16% of patients with neurofibromatosis type 1 (NF1); almost 50% occur in patients with NF1. Deletions of chromosome 22q11–q13 or 17q11 and p53 mutations have been reported. Commonly arises in trunk and extremities and is usually locally invasive. Complete surgical excision is necessary for survival; response to chemotherapy is suboptimal.</td>
</tr>
<tr>
<td>Synovium</td>
<td>Synovial sarcoma</td>
<td>The most common nonrhabdomyosarcoma soft tissue sarcoma in some series. Often manifesting in the 3rd decade, but 33% of patients are younger than age 20 yr. Typically arises around the knee or thigh and is characterized by a nonrandom translocation t(X;18)(p11;q11). Wide surgical excision is necessary. Radiation therapy is effective in microscopic residual disease, and ifosfamide-based therapy is active in advanced disease.</td>
</tr>
<tr>
<td>Unknown</td>
<td>Alveolar soft part sarcoma</td>
<td>Slow-growing tumor; tends to recur or to metastasize to lung and brain years after diagnosis. Often arises in the extremities and head and neck.</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Leiomyosarcoma</td>
<td>Often arises in the gastrointestinal tract and may be associated with a t(12;14)(q14;q23) translocation. Associated with Epstein-Barr virus in immunodeficiency syndromes (including AIDS). Complete surgical excision is the treatment of choice.</td>
</tr>
</tbody>
</table>

Because they are relatively rare in children, much of the information about their natural history and treatment has been derived from studies in adult patients. In children, the median age at diagnosis is 12 yr, with a male:female ratio of 2.3:1. These tumors commonly arise in the trunk or lower extremities. The most common histologic types are synovial sarcoma (42%), fibrosarcoma (13%), malignant fibrous histiocytoma (12%), and neurogenic tumors (10%). Molecular genetic studies often prove useful in diagnosis, because several of these tumors have characteristic chromosomal translocations. Tumor size, stage (clinical group), invasiveness, and histologic grade correlate with survival.

Surgery remains the mainstay of therapy, but a careful search for lung and bone metastases should be undertaken before surgical excision. Chemotherapy and radiation therapy should be considered for large, high-grade, and unresectable tumors. The role of chemotherapy for nonrhabdomyosarcoma soft tissue sarcomas is not as well defined as for rhabdomyosarcoma. Patients with unresectable or metastatic disease are treated with multiagent chemotherapy in addition to irradiation and/or surgery. Patients with completely resected small (<5 cm) tumors are generally treated with surgery alone and can be expected to have an excellent outcome regardless of whether the tumor is high or low grade.

**Prognosis**

Prognostic factors include age, stage, histology, and primary site. Among patients with resectable tumor and favorable histology, 80-90% have prolonged disease-free survival. Unresectable tumor localized to certain favorable sites, such as the orbit, is also a high likelihood of cure. Approximately 65-70% of patients with incompletely resected tumor also achieve long-term disease-free survival. Patients with disseminated disease have a poor prognosis; only approximately 50% achieve remission, and fewer than 50% of these are cured. Older children have a poorer prognosis than younger children. For all patients, surveillance for late effects of cancer treatment is extremely important. Some examples of late effects include infertility from cyclophosphamide, late effects in the radiation field such as bladder dysfunction, infertility, cataracts, impaired bone growth, and secondary malignancies (Table 500-3). Because they are relatively rare in children, much of the information about their natural history and treatment has been derived from studies in adult patients. In children, the median age at diagnosis is 12 yr, with a male:female ratio of 2.3:1. These tumors commonly arise in the trunk or lower extremities. The most common histologic types are synovial sarcoma (42%), fibrosarcoma (13%), malignant fibrous histiocytoma (12%), and neurogenic tumors (10%). Molecular genetic studies often prove useful in diagnosis, because several of these tumors have characteristic chromosomal translocations. Tumor size, stage (clinical group), invasiveness, and histologic grade correlate with survival.

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**Bibliography** is available at Expert Consult.
Bibliography
501.1 Malignant Tumors of Bone

Carola A.S. Arndt

The annual incidence of malignant bone tumors in the United States is approximately 7 cases per 1 million white children younger than 14 yr of age, with a slightly lower incidence in African-American children. Osteosarcoma is the most common primary malignant bone tumor in children and adolescents, followed by Ewing sarcoma (Table 501-1; Fig. 501-1). In children younger than 10 yr of age, Ewing sarcoma is more common than osteosarcoma. Both tumor types are most likely to occur in the second decade of life.

**OSTEOSARCOMA**

**Epidemiology**

The annual incidence of osteosarcoma in the United States is 5.6 cases per 1 million children younger than 15 yr of age. The highest risk period for development of osteosarcoma is during the adolescent growth spurt, suggesting an association between rapid bone growth and malignant transformation. Patients with osteosarcoma are taller than their peers of similar age.

**Pathogenesis**

Although the cause of osteosarcoma is unknown, certain genetic or acquired conditions predispose patients to development of osteosarcoma. Patients with hereditary retinoblastoma have a significantly increased risk for development of osteosarcoma. The sites of osteosarcoma in these patients were initially thought to be only in previously irradiated areas, but later studies show them to arise in sites far from the original retinoblastoma radiation field. Predisposition to development of osteosarcoma in these patients may be related to loss of heterozygosity of the RB gene. Osteosarcoma also occurs in the Li-Fraumeni syndrome, which is a familial cancer syndrome associated with germline mutations of the P53 gene. Kindreds with

<table>
<thead>
<tr>
<th>Table 501-1</th>
<th>Comparison of Features of Osteosarcoma and the Ewing Family of Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEATURE</strong></td>
<td><strong>OSTEOSARCOMA</strong></td>
</tr>
<tr>
<td>Age</td>
<td>Second decade</td>
</tr>
<tr>
<td>Race</td>
<td>All races</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>1.5:1</td>
</tr>
<tr>
<td>Cell</td>
<td>Spindle cell–producing osteoid</td>
</tr>
<tr>
<td>Predisposition</td>
<td>Retinoblastoma, Li-Fraumeni syndrome, Paget disease, radiotherapy</td>
</tr>
<tr>
<td>Site</td>
<td>Metaphyses of long bones</td>
</tr>
<tr>
<td>Presentation</td>
<td>Local pain and swelling; often, history of injury</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td>Sclerotic destruction (less commonly lytic); sunburst pattern</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Ewing sarcoma, osteomyelitis</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Lungs, bones</td>
</tr>
<tr>
<td>Treatment</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Ablative surgery of primary tumor</td>
<td>Radiotherapy and/or surgery of primary tumor</td>
</tr>
<tr>
<td>Outcome</td>
<td>Without metastases, 70% cured; with metastases at diagnosis, ≤20% survival</td>
</tr>
</tbody>
</table>

Figure 501-1 A, Age and skeletal distribution of 1,649 cases of osteosarcoma in the Mayo Clinic files. B, Age and skeletal distribution of 512 cases of Ewing sarcoma in the Mayo Clinic files. (From Unni KK, editor: Dahlin’s bone tumors: general aspects and data on 11,087 cases, ed 5, Philadelphia, 1996, Lippincott-Raven. Reprinted by permission of the Mayo Foundation.)
**Li-Fraumeni syndrome** have a spectrum of malignancies in 1st-degree relatives, including carcinoma of the breast, soft tissue sarcomas, brain tumors, leukemia, adrenal cortical carcinoma, and other malignancies. **Rothmund-Thomson syndrome** is a rare syndrome associated with short stature, skin telangiectasia, small hands and feet, hypoplasia or absence of the thumbs, and a high risk of osteosarcoma. Osteosarcoma also can be induced by irradiation for Ewing sarcoma, craniospinal irradiation for brain tumors, or high-dose irradiation for other malignancies. Other benign conditions that can be associated with malignant transformation to osteosarcoma include Paget disease, enchondromatosis, multiple hereditary exostoses, and fibrous dysplasia.

The pathologic diagnosis of osteosarcoma is made by demonstration of a highly malignant, pleomorphic, spindle cell neoplasm associated with the formation of malignant osteoid and bone. There are 4 pathologic subtypes of conventional high-grade osteosarcoma: osteoblastic, fibroblastic, chondroblastic, and telangiectatic. No significant differences in outcome are associated with the various subtypes, although the chondroblastic component of that subtype may not respond as well to chemotherapy. The role in prognosis of various genes such as drug resistance–related genes, tumor-suppressor genes, and genes related to apoptosis is being evaluated.

**Telangiectatic osteosarcoma** may be confused with aneurysmal bone cyst because of its lytic appearance on radiography. High-grade osteosarcoma typically arises in the diaphyseal region of long bones and invades the medullary cavity. It also may be associated with a soft tissue mass. Two variants of osteosarcoma, parosteal and periosteal osteosarcoma, should be distinguished from conventional osteosarcoma because of their characteristic clinical features. **Parosteal osteosarcoma** is a low-grade, well-differentiated tumor that does not invade the medullary cavity and most commonly is found in the posterior aspect of the distal femur. Surgical resection alone often is curative in this lesion, which has a low propensity for metastatic spread. **Periosteal osteosarcoma** is a rare variant that arises on the surface of the bone but has a higher rate of metastatic spread than the parosteal type and an intermediate prognosis.

### Clinical Manifestations

Pain, limp, and swelling are the most common presenting manifestations of osteosarcoma. Because these tumors occur most often in active adolescents, initial complaints may be attributed to a sports injury or sprain; any bone or joint pain not responding to conservative therapy within a reasonable time should be investigated thoroughly. Additional clinical findings may include limitation of motion, joint effusion, tenderness, and warmth. Results of routine laboratory tests, such as a complete blood cell count and chemistry panel, are usually normal, although alkaline phosphatase or lactate dehydrogenase values may be elevated.

### Diagnosis

Bone tumor should be suspected in a patient who presents with deep bone pain, often causing nighttime awakening, in whom there is a palpable mass and radiographs that demonstrate a lesion. The lesion may be mixed lytic and blastic in appearance, but new bone formation is usually visible. The classic radiographic appearance of osteosarcoma is the sunburst pattern (Fig. 501-2). When osteosarcoma is suspected, the patient should be referred to a center with experience in managing bone tumors. The biopsy and the surgery should be performed by the same surgeon so that the incisional biopsy site can be placed in a manner that will not compromise the ultimate limb salvage procedure. Tissue usually is obtained for molecular and biologic studies at the time of the initial biopsy. Before biopsy, MRI of the primary lesion and the entire bone should be performed to evaluate the tumor for its proximity to nerves and blood vessels, soft tissue and joint extension, and skip lesions. The metastatic work-up, which should be performed before biopsy, includes CT of the chest and radionuclide bone scanning to evaluate for lung and bone metastases, respectively. The **differential diagnosis** of a lytic bone lesion includes histiocytosis, Ewing sarcoma, lymphoma, and bone cyst.

**Figure 501-2** Radiograph of an osteosarcoma of the femur with typical “sunburst” appearance of bone formation.

### Treatment

With chemotherapy and surgery, the 5-yr disease-free survival rate of patients with nonmetastatic extremity osteosarcoma is 65-75%. Complete surgical resection of the tumor is important for cure. The current approach is to treat patients with preoperative chemotherapy in an attempt to facilitate limb salvage operations and to treat micrometastatic disease immediately. Up to 80% of patients are able to undergo limb salvage operations after initial chemotherapy. It is important to resume chemotherapy as soon as possible after surgery. Lung metastases present at diagnosis should be resected by thoracotomies at some time during the course of treatment. Active agents currently in use in multidrug chemotherapy regimens for conventional osteosarcoma include doxorubicin, cisplatin, methotrexate, and ifosfamide.

One of the most important prognostic factors in osteosarcoma is the histologic response to chemotherapy. An international cooperative group is performing a randomized trial of the postoperative addition of high-dose ifosfamide with etoposide to standard 3 drug therapy with cisplatin, doxorubicin, and methotrexate to improve the outcome of patients with a poor histologic response. Patients with a good histologic response were randomized to the addition of pegylated interferon-α2b. Results are anticipated in the near future. For patients with metastatic disease, a new approach is the addition of zoledronic acid, a bisphosphonate, to intensive chemotherapy, with results pending. After limb salvage surgery, intensive rehabilitation and physical therapy are necessary to ensure maximal functional outcome.

For patients who require amputation, early prosthetic fitting and gait training are essential to enable patients to resume normal activities as soon as possible. Before definitive surgery, patients with tumors on weight-bearing bones should be instructed to use crutches to avoid stressing the weakened bones and causing pathologic fracture. The role of chemotherapy in parosteal and periosteal osteosarcomas is not well defined, and chemotherapy is generally reserved for use in patients with tumors which have a high-grade microscopic appearance.
**Prognosis**
Surgical resection alone is curative only for patients with parosteal osteosarcoma. Conventional osteosarcoma requires multiagent chemotherapy. Up to 75% of patients with nonmetastatic extremity osteosarcoma are cured with current multiagent treatment protocols. The prognosis is not as favorable for patients with pelvic tumors as for those with primary tumors in the extremities. Twenty percent to 30% of patients who have limited numbers of pulmonary metastases also can be cured with aggressive chemotherapy and resection of lung nodules. Patients with bone metastases and those with widespread lung metastases have an extremely poor prognosis. Long-term follow-up of patients with osteosarcoma is important to monitor for late effects of chemotherapy, such as cardiotoxicity from anthracycline and hearing loss from cisplatin. Patients in whom late, isolated lung metastases develop may be cured with surgical resection of the metastatic lesions alone.

**EwING SARCOMA**

**Epidemiology**
The incidence of Ewing sarcoma in the United States is 2.1 cases per 1 million children. It is rare among African-American children. Ewing sarcoma, an undifferentiated sarcoma of bone, also may arise from soft tissue. The term **Ewing sarcoma family of tumors** refers to a group of small, round cell, undifferentiated tumors thought to be of neural crest origin that generally carry the same chromosomal translocation. This family of tumors includes Ewing sarcoma of bone and soft tissue and peripheral **primitive neuroectodermal tumor**. Treatment protocols for these tumors are the same whether the tumors arise in bone or soft tissue. Anatomic sites of primary tumors arising in bone are distributed evenly between the extremities and the central axis (pelvis, spine, and chest wall). Primary tumors arising in the chest wall are often referred to as **Askin tumors**.

**Pathogenesis**
Immunohistochemical staining assists in the diagnosis of Ewing sarcoma to differentiate it from small, round, blue cell tumors such as lymphoma, rhabdomyosarcoma, and neuroblastoma. Histochemical stains may react positively with certain neural markers on tumor cells (neuron-specific enolase and S-100), especially in peripheral primitive neuroectodermal tumors. Reactivity with muscle markers (e.g., desmin, actin) is absent. Additionally, MIC-2 (CD99) staining is usually positive. A specific chromosomal translocation, t(11;22), or a variant thereof is found in most of the Ewing sarcoma family of tumors. Analysis for the translocation by FISH (fluorescent in situ hybridization) or polymerase chain reaction analysis for the chimeric fusion gene products EWS/FLI1 or EWS/ERG is utilized routinely in diagnosis.

**Clinical Manifestations**
Symptoms of Ewing sarcoma are similar to those of osteosarcoma. Pain, swelling, limitation of motion, and tenderness over the involved bone or soft tissue are common presenting symptoms. Patients with huge chest wall primary tumors may present with respiratory distress. Patients with paraspinal or vertebral primary tumors may present with symptoms of cord compression. Ewing sarcoma often is associated with **systemic manifestations**, such as fever and weight loss; patients may have undergone treatment for a presumptive diagnosis of osteomyelitis or a fever of unknown origin. Patients also may have a delay in diagnosis when their pain or swelling is attributed to a sports injury.

**Diagnosis**
The diagnosis of Ewing sarcoma should be suspected in a patient who presents with pain and swelling, with or without systemic symptoms, and with a radiographic appearance of a primarily lytic bone lesion with periosteal reaction, the characteristic **onion-skinning** (Fig. 501-3). A large, associated, soft tissue mass often is visualized on MRI or CT (Fig. 501-4). The **differential diagnosis** includes osteosarcoma, osteomyelitis, Langerhans cell histiocytosis, primary lymphoma of bone, metastatic neuroblastoma, or rhabdomyosarcoma in the case of a pure soft tissue lesion. Patients should be referred to a center with
experience in managing bone tumors for evaluation and biopsy. Thorough evaluation for metastatic disease includes CT of the chest, radioisotope bone scan, and bone marrow aspiration and biopsy specimens from at least 2 sites. MRI of the tumor and the entire length of involved bone should be performed to determine the exact extension of the soft tissue and bony mass and the proximity of tumor to neurovascular structures. Fluorodeoxyglucose positron emission tomography scanning is being incorporated to enhance staging. Studies are also using fluorodeoxyglucose positron emission tomography to evaluate response to therapy.

To avoid compromising an ultimate potential for limb salvage by a poorly planned biopsy incision, the same surgeon should perform the biopsy and the surgical procedure. CT-guided biopsy of the lesion often provides diagnostic tissue. It is important to obtain adequate tissue for special stains and molecular studies.

**Treatment**

Tumors of the Ewing sarcoma family are best managed with a comprehensive multidisciplinary approach in which the surgeon, chemotherapist, and radiation oncologist plan therapy. Multiagent chemotherapy is important because it can shrink the tumor rapidly and is usually given before local control is attempted. In North America, standard chemotherapy for nonmetastatic Ewing sarcoma includes vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide. Chemotherapy usually causes dramatic shrinkage of the soft tissue mass and rapid, significant pain relief. The most recent published randomized study for patients with nonmetastatic Ewing sarcoma showed a statistically significantly better outcome when patients were treated on a 14-day schedule than on a 21-day schedule. Current studies are evaluating the addition of topoisomerase inhibitors to standard chemotherapy, and plans are under way to investigate the role of insulin-like growth factor receptor inhibitors for certain groups of patients. An international cooperative group trial is evaluating whether myeloablative chemotherapy and stem cell rescue is superior to chemotherapy with lung irradiation for patients with pulmonary metastases. Ewing sarcoma is considered a radiosensitive tumor, and local control may be achieved with irradiation or surgery. Radiation therapy is associated with a risk of radiation-induced second malignancies, especially osteosarcoma, as well as failure of bone growth in skeletally immature patients. Many centers prefer surgical resection, if possible, to achieve local control. It is important to provide the patient with crutches if the tumor is in a weight-bearing bone, to avoid a pathologic fracture before definitive local control. Chemotherapy should be resumed as soon as possible after surgery.

**Prognosis**

Patients with small, nonmetastatic, distally located extremity tumors have the best prognosis, with a cure rate of up to 75%. Patients with pelvic tumors have, until recently, had a much worse outcome. Patients with metastatic disease at diagnosis, especially bone or bone marrow metastases, have a poor prognosis, with <30% surviving long term. New approaches, such as very intensive chemotherapy with peripheral blood stem cell rescue, are being investigated in these patients.

Long-term follow-up of patients with Ewing sarcoma is important because of the potential for late effects of treatment, such as anthracycline cardiotoxicity; second malignancies, especially in the radiation field; and late relapses, even as long as 10 yr after initial diagnosis.

### 501.2 Benign Tumors and Tumor-Like Processes of Bone

**Carola A.S. Arndt**

Benign bone lesions in children are common in comparison with the relatively rare malignant neoplasms of bone. They present diagnostic challenges. Some, although histologically benign, can be life-threatening. No single element in the history or diagnostic test is sufficient to rule out malignancies or suggest the existence of non-neoplastic conditions. A broad range of diagnostic possibilities must be considered when the physician is confronted with an undiagnosed bone lesion. Benign lesions may be painless or painful, especially if a pathologic fracture is impending. Night pain that awakens a child suggests malignancy, but relief of such pain with aspirin is common with benign lesions such as osteoid osteomas. Rapidly enlarging lesions usually are associated with malignancy, but several benign lesions, such as aneurysmal bone cysts, can enlarge faster than most malignancies. Several conditions, such as osteomyelitis, can simulate the appearance of benign bone tumors.

Many benign bone tumors are diagnosed incidentally or after pathologic fracture. Management of these fractures is similar to that of nonpathologic fractures in the same location. It is unusual for benign bone tumors to interfere with fracture healing. Likewise, the fractures rarely result in changes or healing of these tumors, which usually are treated after the fracture has healed.

Radiographs of any suspected bone lesion should always be obtained in 2 planes. Additional studies may be necessary to help arrive at the correct diagnosis and to guide treatment. Although these lesions are benign, many do require intervention.

**Osteochondroma (exostosis)** is one of the most common benign bone tumors in children. Because many are completely asymptomatic and unrecognized, the true incidence of this lesion is unknown. Most osteochondromas develop in childhood, arising from the metaphysis of a long bone, particularly the distal femur, proximal humerus, and proximal tibia. The lesion enlarges with the child until skeletal maturity. Most are discovered at 3-15 yr of age, when the child or parent notices a bony, nonpainful mass. Some are discovered because they are irritated by pressure during athletic or other activities. Osteochondromas appear radiographically as stalks or broad-based projections from the surface of the bone, usually in a direction away from the adjacent joint. Invariably, the lesion is radiographically smaller than suggested by palpation because the cartilage cap covering the lesion is not seen. This cartilage cap may be up to 1 cm thick. Both the cortex of the bone and the marrow space of the involved bone are continuous with the lesion. Malignant degeneration of a chondrosarcoma is rare in children but occurs in as many as 1% of adults. Routine removal is not performed unless the lesion is large enough to cause symptoms or grows rapidly.

**Multiple hereditary exostoses** is a related but rare condition characterized by the presence of multiple osteochondromas. Severely involved children can have short stature, limb-length inequality, premature partial physeal arrests, and deformity of both the upper and lower extremities. These children must be monitored carefully during growth.

**Enchondroma** is a benign lesion of hyaline cartilage that occurs centrally in the bone. Most of these lesions are asymptomatic and occur in the hands. Most are discovered incidentally, although pathologic fractures often lead to the diagnosis. Radiographically, the lesions occupy the medullary canal, are radiolucent, and are sharply marginated. Punctate or stippled calcification may be present within the lesion, but this is much more common in adults than in children. Almost all enchondromas are solitary. Most can simply be observed, with curettage and bone grafting reserved for lesions that are symptomatic or large enough to weaken the bone structurally. Multifocal involvement is referred to as Maffucci disease and can result in bone dysplasia, short stature, limb-length inequality, and joint deformity. Surgery may be necessary to correct or prevent such deformities. When multiple enchondromas are associated with angiomas of the soft tissue, the condition is referred to as Maffucci syndrome. A high rate of malignant transformation has been reported in both of these multifocal conditions.

**Chondroblastoma** is a rare lesion usually found in the epiphysis of long bones. Most patients present in the 2nd decade with complaints of mild to moderate pain in the adjacent joint. Common sites include the hip, shoulder, and knee. Muscle atrophy and local tenderness may be the only clinical findings. The lesion appears radiographically as a sharply margined radiolucent within the epiphysis or apophysis, occasionally with metaphyseal extension across the physis. Proximity to the joint can cause deformity of the subchondral bone, an effusion, or erosion into the joint. Recognition is important because most lesions
can be cured with curettage and bone grafting before joint destruction occurs.

**Chondromyxoid fibroma** is an uncommon benign bone tumor in children. This metaphyseal lesion usually causes pain and local tenderness. The lesion occasionally is asymptomatic. Chondromyxoid fibroma appears radiographically as eccentric, lobular, metaphyseal radiolucency with sharp, sclerotic, and scalloped margins. The lower extremity is involved most often. Treatment usually consists of curettage and bone grafting or en bloc resection.

**Osteoid osteoma** is a small benign bone tumor. Most of these tumors are diagnosed between 5 and 20 yr of age. The clinical pattern is characteristic, consisting of unremitting and gradually increasing pain that often is worst at night and is relieved by aspirin. Boys are affected more often than girls. Any bone can be involved, but the most common sites are the proximal femur and tibia. Vertebral lesions can cause scoliosis or symptoms that mimic a neurologic disorder. Examination can reveal a limp, atrophy, and weakness when the lower extremity is involved. Palpation and range of motion do not alter the discomfort. Radiographs are distinctive, showing a round or oval metaphyseal or diaphyseal lucency (0.5-1.0 cm in diameter) surrounded by sclerotic bone. The central lucency, or nidus, shows intense uptake on bone scan. Approximately 25% of osteoid osteomas are not visualized on plain radiographs but can be identified with CT. Because of the small size of the lesion and its location adjacent to thick cortical bone, MRI is poor at detecting osteoid osteomas. Treatment is directed at removing the lesion. This can involve en bloc excision, curettage, or percutaneous CT-guided ablation of the nidus. Patients with mild pain may be treated with salicylates. Some lesions resolve spontaneously after skeletal maturity.

**Osteoblastoma** is a locally destructive, progressively growing lesion of bone with a predilection for the vertebrae, although almost any bone may be involved. Most patients note the insidious onset of dull aching pain, which may be present for months before patients seek medical attention. Spinal lesions can cause neurologic symptoms or deficits. The radiographic appearance is variable and less distinctive than that of other benign bone tumors. Approximately 25% show features suggesting a malignant neoplasm, making biopsy necessary in many cases. Expansile spinal lesions often involve the posterior elements. Treatment involves curettage and bone grafting or en bloc excision; care must be taken to preserve nerve roots when treating spinal lesions. Surgical stabilization of the spine may be necessary.

**Fibromas (nonossifying fibroma, fibrous cortical defect, metaphyseal fibrous defect)** are fibrous lesions of bone that occur in 40% of children older than 2 yr of age. They most likely represent a defect in ossification rather than a neoplasm and usually are asymptomatic. Most are discovered incidentally when radiographs are taken for other reasons, usually to rule out a fracture after trauma. Occasional pathologic fractures can occur through rare large lesions. Physical examination usually is unrevealing. Radiographs show a sharply margined eccentric lucency in the metaphyseal cortex. Lesions may be multilocular and expansile, with extension from the cortex into the medullary bone. The long axis of the lesion runs parallel to that of the bone. Approximately 50% are bilateral or multiple. Because of the characteristic radiographic appearance, most lesions do not require biopsy or treatment. Spontaneous regression can be expected after skeletal maturity. Curettage and bone grafting may be recommended for lesions occupying >50% of the bone diameter because of the risk of a pathologic fracture.

**Unicameral bone cysts** can occur at any age in childhood but are rare in children younger than 3 yr of age and after skeletal maturity. The cause of these fluid-filled lesions is unknown. Some resolve spontaneously after skeletal maturity is reached. Most are asymptomatic until diagnosis, which usually follows a pathologic fracture. Such fractures can occur with relatively minor trauma, such as with throwing or catching a ball. Unicameral bone cysts appear radiographically as solitary, centrally located lesions within the medullary portion of the bone. These cysts are most common in the proximal humerus or femur. They often extend to (but not through) the physis and are sharply marginated. The cortex expands, but that does not exceed the width of the adjacent physis. Treatment involves allowing the pathologic fracture to heal, followed by aspiration and injection with methylprednisolone or bone marrow. Repeat injections, curettage, and bone grafting occasionally are necessary to treat recurrent lesions.

**Aneurysmal bone cyst** is a reactive lesion of bone seen in persons younger than 20 yr of age. The lesion is characterized by cavernous spaces filled with blood and solid aggregates of tissue. Although the femur, tibia, and spine are most commonly involved, this progressively growing, expansile lesion develops in any bone. Pain and swelling are common. Spinal involvement can lead to cord or nerve root compression and associated neurologic symptoms, including paralysis. Radiographs show eccentric lytic destruction and expansion of the metaphysis surrounded by a thin sclerotic rim of bone. Posterior elements of the spine are involved more commonly than the vertebral body. Unlike most other benign bone tumors, which usually are confined to a single bone, aneurysmal bone cysts can involve adjacent vertebrae. Rapid growth is characteristic and can lead to confusion with malignant neoplasms. Treatment consists of curettage and bone grafting or excision. Spinal lesions can require stabilization after excision. As with other benign tumors, attempts are made to preserve nerve roots and other vital structures. Recurrence after surgical treatment occurs in 20-30% of patients, is more common in younger than older children, and usually occurs in the 1st 1-2 yr after treatment.

**Fibrous dysplasia** is a developmental abnormality characterized by fibrous replacement of cancellous bone. Lesions may be solitary or multifocal (polyostotic), relatively stable, or progressively more severe. Most children are asymptomatic, although those with skull involvement might have swelling or exophthalmos. Pain and limp are characteristic of proximal femoral involvement. Limb-length discrepancy, bowing of the tibia or femur, and pathologic fractures may be presenting complaints. The triad of polyostotic disease, precocious puberty, and cutaneous pigmentation is known as Albright syndrome. Radiographic features of fibrous dysplasia include a lytic or ground-glass expansile lesion of the metaphysis or diaphysis. The lesion is sharply marginated and often is surrounded by a thick rim of sclerotic bone. Bowing, especially of the proximal femur, may be present. Treatment usually involves observation. Surgery is indicated for patients with progressive deformity, pain, or impending pathologic fractures. Bone grafting is not as successful in the treatment of fibrous dysplasia as with other benign tumors, because the lesion often recurs within the grafted bone. Reconstructive surgical techniques often are necessary to provide stability.

**Osteofibrous dysplasia** affects children 1-10 yr of age. This lesion usually involves the tibia. It is clinically, radiographically, and histologically distinct from fibrous dysplasia. Most children present with anterior swelling or enlargement of the leg. Progression is unlikely after 10 yr of age. Radiographs show solitary or multiple lucent cortical diaphyseal lesions surrounded by sclerosis. Anterior bowing of the tibia is often present. The radiographic appearance closely resembles that of adamantinoma, a malignant neoplasm, making biopsy more common than with other benign bone tumors. Treatment involves observation. Some lesions heal spontaneously. Excision and bone grafting should be delayed until the child is older than 10 yr of age because of a high recurrence rate before this age. Pathologic fractures heal with immobilization.

**Langerhans cell histiocytosis** is a monostotic or polyostotic disease that can also involve the skin, liver, or other organs. Single-site disease should be distinguished from the other forms of Langerhans cell histiocytosis (Hand-Schüller-Christian or Letterer-Siwe variants), which can have a less favorable prognosis (see Chapter 507). Langerhans cell histiocytosis usually occurs during the 1st 3 decades of life and is most common in boys 5-10 yr of age. The skull is most commonly affected, but any bone may be involved. Patients usually present with local pain and swelling. Marked tenderness and warmth often are present in the area of the involved bone. Spinal lesions can cause pain, stiffness, and occasional neurologic symptoms. The radiographic appearance of the skeletal lesions is similar in all forms of Langerhans cell histiocytosis but is variable enough to mimic many other benign and malignant lesions of bone. The radiolucent lesions have well-defined or irregular margins with expansion of the involved bone and peristomal new bone formation. Spine involvement can cause uniform compression or flattening of the vertebral body. A skeletal survey is warranted because
polyostotic involvement and the typical skull lesions strongly suggest the diagnosis of eosinophilic granuloma. Biopsy often is necessary to confirm the diagnosis because of the broad radiographic differential diagnosis. Treatment includes curettage and bone grafting, low-dose radiation therapy, or corticosteroid injection. Observation for symptomatic lesions is reasonable because most osseous lesions heal spontaneously and do not recur. Children with bone lesions should be evaluated for visceral involvement because treatment of Hand-Schüller-Christian disease and Letterer-Siwe disease is more complex and often systemic.

Bibliography is available at Expert Consult.
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Retinoblastoma is an embryonal malignancy of the retina and the most common intraocular tumor in children. Although the survival rate of children in the United States and developed countries with retinoblastoma is extremely high, retinoblastoma progresses to metastatic disease and death in over 50% of children worldwide. Furthermore, the associated loss of vision and side effects of therapy are significant problems that remain to be addressed.

**EPIDEMIOLOGY**

Approximately 250-350 new cases of retinoblastoma are diagnosed each year in the United States, with no known racial or gender predilection. The cumulative lifetime incidence of retinoblastoma is approximately 1:20,000 live births, and retinoblastoma accounts for 4% of all pediatric malignancies. The median age at diagnosis is approximately 2 yr, and more than 90% of cases are diagnosed in children younger than 5 yr of age. Overall, about 66-75% of children with retinoblastoma have unilateral tumors, with the remainder having bilateral retinoblastoma. Bilateral involvement is more common in younger children, particularly in those diagnosed younger than the age of 1 yr, and is always heritable. There is a possible increased risk of retinoblastoma in children conceived by in vitro fertilization.

Retinoblastoma can be either hereditary or sporadic. Hereditary cases usually are diagnosed at a younger age and are multifocal and bilateral, whereas sporadic cases are usually diagnosed in older children who tend to have unilateral, unifocal involvement. The hereditary form is associated with loss of function of the *retinoblastoma gene (RB1)* via gene mutation or deletion. The *RB1* gene is located on chromosome 13q14 and encodes the *retinoblastoma protein*, a tumor-suppressor protein that controls cell-cycle phase transition and has roles in apoptosis and cell differentiation. Many different causative mutations have been identified, including translocations, deletions, insertions, point mutations, and epigenetic modifications such as gene methylation. The nature of the predisposing mutation can affect the penetrance and expressivity of retinoblastoma development.

According to Knudson’s “two-hit” model of oncogenesis, 2 mutational events are required for retinoblastoma tumor development (see Chapter 492). In the hereditary form of retinoblastoma, the first mutation in the *RB1* gene is inherited through germinal cells and a second mutation occurs subsequently in somatic retinal cells. Second mutations that lead to retinoblastoma often result in the loss of the normal allele and concomitant loss of heterozygosity. Parents and siblings of a child with a germline mutation should be referred to a genetic specialist for testing; most children with hereditary retinoblastoma have spontaneous new germinal mutations, and both parents have wild-type retinoblastoma genes. All 1st-degree relatives of children with known or suspected hereditary retinoblastoma should have retinal examinations to identify retinomas or retinal scars, which may suggest hereditary retinoblastoma even though malignant retinoblastoma did not develop. In the sporadic form of retinoblastoma, the 2 mutations occur in somatic retinal cells. Heterozygous carriers of oncogenic *RB1* mutations demonstrate variable phenotypic expression.

**PATHOGENESIS**

Histologically, retinoblastoma appears as a small round blue cell tumor with rosette formation (Flexner-Wintersteiner rosettes). It may arise in any of the nucleated layers of the retina and exhibit various degrees of differentiation. Retinoblastoma tumors tend to outgrow their blood supply, resulting in necrosis and calcification.

Endophytic tumors arise from the inner surface of the retina and grow into the vitreous, and can also grow as tumors suspended within the vitreous itself, known as vitreous seeding. Exophytic tumors grow from the outer retinal layer and can cause retinal detachment. Diffuse infiltrating tumors grow intraretinally and remain flat; these are less common and can cause iris neovascularization. Tumors can also be both endophytic and exophytic. These tumors can also spread by direct extension to the choroid or along the optic nerve beyond the lamina cribrosa to the central nervous system, or by hematogenous or lymphatic spread to distant sites, including bones, bone marrow, and lungs.

**CLINICAL MANIFESTATIONS**

Retinoblastoma classically presents with leukocoria, a white pupillary reflex (Fig. 502-1), which often is first noticed when a red reflex is not present at a routine newborn or well-child examination or in a flash photograph of the child. Strabismus often is an initial presenting complaint. Decreased vision, orbital inflammation, hyphema, and pupil irregularity can occur with advancing disease. Pain can occur if secondary glaucoma is present. Only approximately 10% of retinoblastoma cases are detected by routine ophthalmologic screening in the context of a positive family history.

**DIAGNOSIS**

The diagnosis is established by the characteristic ophthalmologic findings of a chalky, white-gray retinal mass with a soft, friable consistency.

![Image of retinoblastoma](image-url)

**Figure 502-1 A, Leukocoria noted in the left eye of a child presenting with retinoblastoma. B, A large white tumor mass noted within the posterior chamber of the enucleated eye. (From Shields JA, Shields CL: Current management of retinoblastoma, Mayo Clin Proc 69:50–56, 1994.)**
Other radiation-related late adverse effects include cataracts, orbital growth deformities, lacrimal dysfunction, and late retinal vascular injury.

Bibliography is available at Expert Consult.
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EPIDEMIOLOGY
Malignant germ cell tumors (GCTs) and gonadal tumors are rare, with an incidence of 12 cases per 1 million persons younger than 20 yr of age. Most malignant tumors of the gonads in children are GCTs. The incidence varies according to age and sex, although the incidence of GCTs in adolescent males has increased over time. Sacrococcygeal tumors occur predominantly in infant girls. Testicular GCTs occur predominantly before age 4 yr and after puberty. Klinefelter syndrome is associated with an increased risk of mediastinal GCTs; Down syndrome, undescended testes, infertility, testicular atrophy, testicular microliithiasis, testicular dysgenesis syndrome, and inguinal hernias are associated with an increased risk of testicular cancer. The risk of testicular cancer in patients with cryptorchidism is reduced but not eliminated if orchiopexy is performed before 13 yr of age. The risk of testicular GCT is increased in 1st-degree relatives and is highest among monozygotic twins.

PATHOGENESIS
The GCTs and non-GCTs arise from primordial germ cells and coelomic epithelium, respectively. Testicular and sacrococcygeal GCTs arising during early childhood characteristically have deletions at chromosome arms 1p and 6q and gains at 1q, and lack the isochromosome 12p that is highly characteristic of malignant GCTs of adults. Testicular GCT also may demonstrate loss of imprinting. Ovarian GCTs from older girls characteristically have deletions at 1p and gains at 1q and 21. Because GCTs may contain benign and mixed malignant elements in different areas of the tumor, extensive sectioning is essential to confirm the correct diagnosis. The many histologically distinct subtypes of GCTs include teratoma (mature and immature), endodermal sinus tumor, and embryonal carcinoma (Fig. 503-1). Non-GCTs of the ovary include epithelial (serous and mucinous) and sex cord–stromal tumors; non-GCTs of the testicle include sex cord/stromal (e.g., Leydig cell, Sertoli cell) tumors. Dicer1 mutations have been observed in nonepithelial ovarian cancers, especially in Sertoli-Leydig tumors.

CLINICAL MANIFESTATIONS AND DIAGNOSIS
The clinical presentation of germ cell neoplasms depends on location. Ovarian tumors often are quite large by the time they are diagnosed (Fig. 503-2). Extragonadal GCTs occur in the midline, including the suprasellar region, pineal region, neck, mediastinum, and retroperitoneal and sacrococcygeal areas (Fig. 503-3). Symptoms relate to mass effect, but the intracranial GCTs often present with anterior and posterior pituitary deficits (see Chapter 497).

The serum α-fetoprotein (AFP) level is elevated with endodermal sinus tumors and may be minimally elevated with teratomas. Infants normally have higher levels of AFP, which fall to normal adult levels by about age 8 mo; consequently, high AFP levels must be interpreted with caution in this age group. Elevation of the β subunit of human chorionic gonadotropin, which is secreted by syncytiotrophoblasts, is seen with choriocarcinoma and germinomas. Lactate dehydrogenase,
Gonadoblastomas often occur in patients with gonadal dysgenesis and all or parts of a Y chromosome. Gonadal dysgenesis is characterized by failure to fully masculinize the external genitalia. If this syndrome is diagnosed, imaging of the gonad with ultrasonography or CT is performed, and surgical resection of the tumor usually is curative. Prophylactic resection of dysgenetic gonads at the time of diagnosis is recommended, because gonadoblastomas, some of which contain malignant GCT elements, often develop. Gonadoblastomas may produce abnormal amounts of estrogen.

Teratomas occur in many locations, presenting as masses. They are not associated with elevated markers unless malignancy is present. The sacrococcygeal region is the most common site for teratomas. Sacrococcygeal teratomas occur most commonly in infants and may be diagnosed in utero or at birth, with most found in girls. The rate of malignancy in this location varies, ranging from <10% in children younger than 2 mo of age to >50% in children older than 4 mo of age.

Germinomas occur intracranially, in the mediastinum, and in the gonads. In the ovary, they are called dysgerminomas; in the testis,
**Seminomas.** They usually are tumor-marker–negative masses despite being malignant. Endodermal sinus or yolk sac tumor and choriocarcinoma appear highly malignant by histologic criteria. Both occur at gonadal and extragonadal sites. Embryonal carcinoma most often occurs in the testes. Choriocarcinoma and embryonal carcinoma rarely occur in the pure form and are usually found as part of a mixed malignant GCT.

**Non–germ cell gonadal tumors** are very uncommon in pediatrics and occur predominantly in the ovary. Epithelial carcinomas (usually an adult tumor), Sertoli-Leydig cell tumors, and granulosa cell tumors may occur in children. Carcinomas account for about one third of ovarian tumors in females younger than 20 yr of age; most of these occur in older teens and are of the serous or mucinous subtype. Sertoli-Leydig cell tumors and granulosa cell tumors produce hormones that can cause virilization, feminization, or precocious puberty, depending on pubertal stage and the balance between Sertoli cells (estrogen production) and Leydig cells (androgen production). Diagnostic evaluation usually focuses on the chief complaint of inappropriate sex steroid effect and includes hormone measurements, which reflect gonadotropin-independent sex steroid production. Appropriate imaging also is performed to rule out a functioning gonadal tumor. Surgery usually is curative. No effective therapy for nonresectable disease has been found.

**TREATMENT**
Complete surgical excision of the tumor usually is indicated, except for patients with intracranial tumors, where the primary therapy consists of radiation therapy and chemotherapy. For testicular tumors, an inguinal approach is indicated, and complete resection should include the entire spermatic cord. When complete excision cannot be accomplished, preoperative chemotherapy is indicated, with second-look surgery. For completely resected nonseminomatous testicular tumors, there is debate on whether patients can be clinically observed following surgery. For teratomas, both mature and immature, and completely resected malignant tumors of the testes, surgery alone is the treatment. For ovarian tumors, unless the contralateral ovary is obviously also involved by tumor, a fertility-sparing surgery should be performed. Cisplatin-based chemotherapy regimens usually are curative in GCTs that cannot be completely resected, even if metastases are present. However, sex cord–stromal tumors tend to be refractory to chemotherapy. Except for GCTs of the central nervous system, radiation therapy is limited to those tumors that are not amenable to complete excision and are refractory to chemotherapy.

**PROGNOSIS**
The overall cure rate for children with GCTs is >80%. Age is the most predictive factor of survival for extragonadal GCTs. Children older than 12 yr of age have a 4-fold higher risk of death, and a 6-fold higher risk if the tumor is thoracic. Histology has little effect on prognosis. Nonresected extragonadal GCTs have a slightly worse prognosis.

*Bibliography is available at Expert Consult.*
Bibliography
Hepatic tumors are rare in children. Primary tumors of the liver account for approximately 1% of malignancies in children younger than 15 yr of age, with an annual incidence of 1.6 cases per 1 million children in the United States. Between 50% and 60% of hepatic tumors in children are malignant, with >65% of these malignancies being hepatoblastomas and most of the remainder being hepatocellular carcinomas. Rare hepatic malignancies include embryonal sarcoma, angiosarcoma, malignant germ cell tumor, rhabdomyosarcoma of the liver, and undifferentiated sarcoma. More common childhood malignancies, such as neuroblastoma, Wilms tumor, and lymphoma, can metastasize to the liver. Benign liver tumors, which usually present in the 1st 6 mo of life, include hemangiomas, hamartomas, and hemangioendotheliomas.

**HEPATOBLASTOMA**

**Epidemiology**

Approximately 100 new cases of hepatoblastoma are diagnosed each yr in the United States. Hepatoblastoma occurs predominantly in children younger than 3 yr of age and the median age of diagnosis is 1 yr. The etiology is unknown. Hepatoblastomas are associated with familial adenomatous polyposis. Alterations in the antigen-presenting cell/β-catenin pathway have been found in most of the tumors evaluated. Hepatoblastomas are also associated with Beckwith-Wiedemann syndrome, hemihyperplasia, and other somatic overgrowth syndromes. Increased expression of insulin-like growth factor 2 secondary to genetic mutations or epigenetic changes is implicated in hepatoblastoma development in patients with Beckwith-Wiedemann syndrome. All children with Beckwith-Wiedemann syndrome or hemihyperplasia should be routinely screened with α-fetoprotein (AFP) levels and abdominal ultrasounds. Prematurity and low birthweight is associated with increased incidence of hepatoblastoma, with the risk increasing as birthweight decreases.

**Pathogenesis**

Hepatoblastoma arises from precursors of hepatocytes and is histologically classified as whole epithelial type, containing fetal or embryonal malignant cells (either as a mixture or as pure elements), and mixed type, containing both epithelial and mesenchymal elements. Histologic classification has a direct correlation with clinical outcome. The pure fetal histology subtype predicts a more favorable outcome and the small cell undifferentiated subtype is associated with normal AFP levels and predicts a worse outcome.

**Clinical Manifestations**

Hepatoblastoma usually presents as a large, asymptomatic abdominal mass. It arises from the right lobe 3 times more often than the left and usually is unifocal. As the disease progresses, fatigue, fever, weight loss, anorexia, vomiting, and abdominal pain may ensue. Rarely, hepatoblastoma presents with hemorrhage secondary to trauma or spontaneous rupture. Metastatic spread of hepatoblastoma most commonly involves regional lymph nodes and the lungs.

**Diagnosis**

A biopsy of liver tumors is necessary to establish the diagnosis. A valuable serum tumor marker, AFP, is used in the diagnosis and monitoring of hepatic tumors. The AFP levels are elevated in almost all hepatoblastomas. Bilirubin and liver enzymes usually are normal. Anemia is common, and thrombocytosis occurs in approximately 30% of patients. Serologic testing for hepatitides B and C should be performed, but the results usually are negative in hepatoblastoma.

Diagnostic imaging should include plain radiographs and ultrasonography of the abdomen to characterize the hepatic mass. Ultrasonography can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest.

**Treatment**

In general, the cure of malignant hepatic tumors in children depends on complete resection of the primary tumor (Fig. 504-1); as much as 85% of the liver can be resected, with hepatic regeneration noted within 3-4 mo after surgery. Treatment of hepatoblastoma is based on surgery and systemic chemotherapy using cisplatin in combination with vincristine and 5-fluorouracil or doxorubicin. In 30% of cases,
tumors are resectable at diagnosis; a safe attempt for initial gross total resection should be made followed by adjuvant chemotherapy. Unresectable tumors with or without metastatic disease, at presentation, usually respond to chemotherapy; preoperative chemotherapy is indicated, and excision of the primary tumor and extrahepatic disease should be attempted as soon as it becomes feasible, followed by additional chemotherapy. Liver transplant is a viable option for unresectable tumors with or without metastatic disease, resulting in survival rates of approximately 25%. Treatment-related long-term adverse effects include cardiac toxicity with doxorubicin and renal and ototoxicity with cisplatin.

HEPATOCELLULAR CARCINOMA

Epidemiology
Hepatocellular carcinoma occurs mostly in adolescents and often is associated with hepatitis B or C infection. It is more common in East Asia and other areas where hepatitis B is endemic; the incidence has decreased following the introduction of hepatitis B vaccination. In these areas it also tends to occur in a bimodal pattern, with the younger age peak overlapping the age of hepatoblastoma presentation. It also occurs in the chronic form of hereditary tyrosinemia, galactosemia, glycogen storage disease, α1-antitrypsin deficiency, and biliary cirrhosis. Aflatoxin B contamination of food is another risk factor.

Pathogenesis
Hepatocellular carcinoma usually arises in an abnormal or cirrhotic liver and presents as a multicentric, invasive tumor consisting of large pleomorphic cells of epithelial origin. Compared to adults, cirrhosis in children is less common and congenital liver disorders are more common. Hepatocellular carcinomas are classified as classical or fibrolamellar. The fibrolamellar variant occurs more often in adolescent and young adult patients and is not associated with cirrhosis. Although previous reports have suggested that the fibrolamellar type has a better prognosis, more recent data analysis refutes this.

Clinical Manifestations
Hepatocellular carcinoma usually presents as a hepatic mass with abdominal distention and symptoms of anorexia, weight loss, and abdominal pain. Hepatocellular carcinoma can present as an acute abdominal crisis with rupture of the tumor and hemoperitoneum. Metastatic spread usually involves regional lymph nodes and the lungs. The AFP level is elevated in approximately 60% of children. Evidence of hepatitides B and C infection usually is found in endemic areas but not in Western countries or with the fibrolamellar type. Bilirubin usually is normal, but liver enzymes may be abnormal.

Diagnostic imaging should include plain radiographs and ultrasonography of the abdomen to characterize the hepatic mass. Ultrasonography can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest.

Treatment
Complete tumor resection is crucial for curative treatment. Because of the multicentric origin of hepatocellular carcinoma and underlying liver disease, complete resection is accomplished in only 30-40% of cases. A gross total resection should be attempted at diagnosis when possible; combination chemotherapy following surgery is necessary. For unresectable tumors, chemotherapy followed by surgical assessment is essential; liver transplant is an option for unresectable tumors. Even with complete surgical resection, only 30% of children are long-term survivors. Chemotherapy, including cisplatin, doxorubicin, etoposide, and 5-fluorouracil, has shown some activity against this tumor, but improved long-term outcome has been difficult to achieve. Other techniques, such as cryosurgery, radiofrequency ablation, transarterial chemoembolization, and ethanol injection, are under study as therapy for hepatocellular carcinomas.

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


Benign Vascular Tumors

505.1 Hemangiomas

Cynthia E. Herzog

Hemangiomas, the most common benign tumors of infancy, occur in approximately 5-10% of term infants (see Chapter 650). The risk of hemangioma is 3-5 times higher in girls than boys. The risk is doubled in premature infants and 10 times higher in offspring of women who had chorionic villus sampling. Hemangiomas can be present at birth but usually arise shortly after birth and grow rapidly during the 1st yr of life, with slowing of growth in the next 5 yr and involution by 10-15 yr of age.

CLINICAL MANIFESTATIONS

More than 50% of all hemangiomas are located in the head and neck region. Most are solitary lesions, but the presence of more than 1 cutaneous lesion increases the likelihood of visceral hemangiomas. The liver is the primary site of visceral involvement; other involved organs include the brain, intestines, and lung. Infantile hemangiomas can be differentiated from other lesions with which they may be confused by the expression of GLUT1. Most hemangiomas require no therapy, but approximately 10% of hemangiomas cause significant impairment and 1% are life-threatening because of their location. Hemangiomas around the airway can cause airway obstruction, and those around the eyes can result in loss of vision. Ulceration is a common complication and can lead to secondary infection. With or without treatment, after involution of a hemangioma, residual skin abnormalities remain. Large hepatic hemangiomas or hemangioendotheliomas may result in hepatomegaly, anemia, thrombocytopenia, and high-output heart failure.

Kasabach-Merritt syndrome (see Chapter 650) is characterized by a rapidly enlarging lesion, thrombocytopenia, microangiopathic hemolytic anemia, and coagulopathy as a result of platelet and red blood cell trapping and activation of the clotting system within the vasculature of the hemangioma. This syndrome is associated with kaposiform hemangioendotheliomas or tufted angiomas but not with infantile hemangiomas.

Cutaneous lesions usually can be diagnosed by typical appearance and rapid proliferation. Segmental hemangiomas, or those with geographic localization and some plaque-like features, recently have been shown to have a higher risk of complications and association with developmental abnormalities. A deep lesion may require imaging studies to help differentiate it from a lymphangioma. The presence of a midline hemangioma in the lumbosacral area indicates the need for an MRI to search for underlying asymptomatic neurologic abnormalities. Location also may dictate the need for an ophthalmologic or surgical consultation. An ultrasonographic scan or MRI of the liver should be performed if multiple cutaneous lesions are present.

TREATMENT

See Chapter 650.

Bibliography is available at Expert Consult.

505.2 Lymphangiomas and Cystic Hygromas

Cynthia E. Herzog

Lymphatic malformations, including lymphangiomas and cystic hygromas, which arise in the embryonic lymph sac, are the second most common benign vascular tumors in children. About half are located in the head and neck area. Approximately 50% are present at birth, with most presenting by 2 yr of age. There is no gender predisposition. Spontaneous regression has been reported but is not typical.

Lymphatic malformations present as soft, painless masses that transilluminate if superficial. Intrathoracic lymphatic malformation can present as symptoms related to a mediastinal mass or pericardial or pleural effusion. Rapid enlargement can occur with infection or hemorrhage. Localized lesions may be surgically resected, but this can be difficult, owing to their infiltrative nature. Recurrence is common with incompletely resected lesions. Aspiration can provide temporary relief in an emergency, such as in the presence of dyspnea, but reaccumulation will occur. Treatment by injection of sclerosing agents, laser therapy, and systemic interferon therapy also has been used. The streptococcal immunotherapeutic agent OK-432 (Picibanil) is the sclerosing agent of choice; its use will prevent the need for surgery in most cases. Bleomycin is also an effective sclerosing agent but has a risk of pulmonary toxicity. It appears to be especially effective for the treatment of macrocystic lymphangiomas of the head and neck.

Bibliography is available at Expert Consult.
Bibliography


Bibliography
BENIGN THYROID TUMORS
Benign thyroid tumors represent approximately 75% of all thyroid nodules presenting in the pediatric population. The work-up of a suspected thyroid nodule includes the laboratory assessment of thyroid function, ultrasound to assess the nodule and regional lymph node characteristics, and fine-needle aspiration biopsy under ultrasound guidance for definitive pathologic diagnosis. Nuclear scintigraphy using radioactive iodine ($^{123}$I) or $^{99m}$Tc-pertechnetate is not recommended in the initial diagnostic evaluation, except in the event of a suppressed thyroid-stimulating hormone (TSH) level.

MALIGNANT THYROID TUMORS
Pediatric thyroid malignancies are rare tumors that include medullary thyroid carcinoma (MTC) and the differentiated thyroid carcinomas (DTCs): papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma. PTC represents the vast majority of thyroid cancers in children, who have an excellent overall prognosis with anticipated survival over decades, even in the presence of metastatic disease at diagnosis. The major established environmental risk factor for the development of PTC is exposure to ionizing radiation.

MTC is a very uncommon disease in childhood that almost always occurs in the context of an autosomal dominant, hereditary endocrine tumor syndrome that arises secondary to activating mutations in the RET (REarranged during Transfection) protooncogene: multiple endocrine neoplasia type 2a (MEN2A) or type 2b (MEN2B). In addition to the almost complete penetrance of MTC in the most common RET mutations, patients with MEN2A and MEN2B have up to a 50% lifetime risk of developing pheochromocytomas. Up to 20% of MEN2A patients will develop primary hyperparathyroidism. Patients with MEN2B do not develop hyperparathyroidism but have a distinct phenotype with a characteristic facial appearance, marfanoid body habitus, and a generalized ganglioneuromatosis, manifested most obviously by the presence of oral mucosal neuromas (Fig. 506-1). The
pathognomonic phenotype of MEN2B is not apparent in very early childhood, although an inability to cry tears and constipation represent early clues to diagnosis in these patients.

Children with thyroid cancer usually present with an asymptomatic thyroid mass and/or cervical lymphadenopathy, although children with MEN2 are often diagnosed only after a positive genetic test result or, in the case of MEN2B, after the clinical phenotype is recognized. Lymph node metastases are present in the majority of PTC cases and lung metastases are identified in up to 20% of patients, primarily in those children with a high burden of neck disease.

The primary therapy for thyroid cancer is a total thyroidectomy and a compartment-oriented lymph node dissection, as indicated, performed by a highly experienced thyroid cancer surgeon. In DTC, 131I is used postoperatively to treat distant metastasis and unresectable residual neck disease. In PTC, the routine use of 131I is limited to those children who are most likely to benefit from treatment. Children with MTC do not require 131I therapy. The TSH level is initially suppressed by giving supraphysiologic levothyroxine in the case of DTC, as TSH stimulates DTC tumor growth; the TSH is kept normal in the case of MTC. Long-term follow-up involves monitoring of tumor markers (thyroglobulin in DTC and calcitonin/carcinogenic embryonic antigen in MTC), as well as routine imaging, primarily neck ultrasound.

In MEN2, there are well-documented genotype-phenotype correlations, and the biologic aggressiveness of MTC depends on the hereditary setting in which it develops. With the advent of genetic testing for RET mutations, MTC has become one of the few malignancies that can be cured via early thyroidectomy before the cancer becomes metastatic. Recommendations regarding the age at surgery of children who are carriers of a RET mutation are evolving and incorporate clinical testing (ultrasound and calcitonin levels) in addition to knowledge regarding the genotype. Novel oral tyrosine kinase inhibitors are approved by the FDA for the treatment of advanced MTC and DTC in adults.

Figure 506-1 Classic appearance of oral mucosal neuromas on the tongue in a boy with MEN2B secondary to the typical M918T mutation in the RET protooncogene.

Bibliography is available at Expert Consult.

506.2 Melanoma

Dennis P.M. Hughes and Cynthia E. Herzog

See Chapter 651.

The incidence of melanoma in persons younger than 20 yr of age in the United States is 4.2 cases per 1 million, with 73% occurring in 15-19 year olds, 17% in 10-14 year olds, and 10% occurring in children younger than 10 yr of age (see Chapter 651). Melanoma is more common among adolescent females than males. In the United States, incident rates of melanoma in younger age groups are increasing, although at a slower rate than in adults. UV light, especially sun exposure, is a well-known risk factor for melanoma in adults, and also contributes to teenage melanoma, as shown by the tendency of lesions to develop on sun-exposed areas in this age group. In younger patients, melanoma does not appear to be associated with sun exposure and often occurs in skin that is not frequently exposed to the sun. Pediatricians should counsel patients regarding avoidance of sun exposure and the use of tanning beds to decrease the risk of later development of melanoma. Patients with fair skin and a family history of melanoma are at particularly high risk. Known risk factors for children are a giant hairy nevus (>10 cm), dysplastic nevus syndrome, and xeroderma pigmentosum. These conditions merit total skin examination at least annually.

Findings of a rapidly enlarging nevus that is dark, has changed colors, has irregular borders, or bleeds easily should raise a concern of melanoma. However, more than half of pediatric melanomas are nonpigmented, and can easily be confused with a wart or other benign finding. Diagnosis is based on pathology, and a punch biopsy is preferred. However, extra care must be taken in the diagnosis of melanoma in children because making the distinction from other lesions, particularly Spitz nevus, can be difficult. Management in a center with expertise in pediatric melanoma may be advisable, especially for anything other than thin melanomas (Breslow thickness of 1 mm or greater).

Prognosis and treatment recommendations have previously been extrapolated from adult data; however, specific prognostic factors for pediatric melanoma are starting to accrue. The initial diagnosis is best made with a punch biopsy. Shave biopsy is specifically discouraged, as this method tends to leave the base of the lesion behind, and specific information about the depth of invasion is lost. Biopsy sites that test positive for melanoma should be reexcised with appropriate margins based on thickness. Lymph node mapping and sentinel node biopsy should also be performed for all melanomas with a Breslow thickness >0.5-1 mm, or any lesions in which the tumor base was not resected. If the sentinel node is positive, a formal lymph node dissection is essential for ensuring the best probability of survival. To date, the treatment of childhood melanoma still mirrors treatment of adult melanoma. High-dose adjuvant interferon shows some efficacy in the treatment of adult melanoma, whereas chemotherapy in combination with biologic agents and vaccine therapy has been used for treatment of distant metastases. Although novel therapies such as targeted B-Raf inhibitors and immune-modulating agents have received regulatory approval for treatment of adult melanoma, their use in children is still investigational.

Bibliography is available at Expert Consult.

506.3 Nasopharyngeal Carcinoma

Cynthia E. Herzog

Nasopharyngeal carcinoma is rare in the pediatric population but is one of the most common nasopharyngeal tumors in pediatric patients. In adults, the incidence is highest in South China, but it is also high among the Inuit people and in North Africa and Northeast India. In China, it is rare in the pediatric population, but in other populations a substantial proportion of cases occur in the pediatric age group, primarily in adolescents. It occurs in males twice as often as in females and is more common in blacks. In the pediatric population the tumors are more commonly of undifferentiated histology and associated with Epstein-Barr virus. Nasopharyngeal carcinoma is associated with specific human leukocyte antigen types, and other genetic factors may play a role, especially in low-incidence populations.

Most pediatric patients present with advanced locoregional disease manifesting as cervical lymphadenopathy. Epistaxis, trismus, and cranial nerve deficits also may be present. The diagnosis is established from biopsy of the nasopharynx or cervical lymph nodes. In most cases the lactate dehydrogenase level is elevated, but this finding is nonspecific. CT or MRI evaluation of the head and neck is performed to
Bibliography
Bibliography
determine the extent of locoregional disease. Chest radiography, CT, bone scan, and liver scan are used to evaluate for metastatic disease. Positron emission tomography scans appear to be useful for monitoring both primary disease and looking for metastases. Epstein-Barr virus DNA levels correlate with disease stage, have prognostic value, and can be used to monitor for recurrence.

Treatment is a combination of chemotherapy and irradiation. Cisplatin given concurrently with radiation, with or without neoadjuvant cisplatin-based chemotherapy, is the standard treatment. The outcome depends on the extent of disease; patients with distant metastases have a very poor prognosis. Using intensity-modulated radiation therapy improves local control and reduces the late adverse effects associated with radiation therapy, including hormonal dysfunction, dental caries, fibrosis, and second malignancies. Use of proton therapy may result in further reduction of adverse effects.

Bibliography is available at Expert Consult.

506.4 Adenocarcinoma of the Colon and Rectum

Cynthia E. Herzog and Winston W. Huh

Colorectal carcinoma (CRC) is rare in the pediatric population with an estimated incidence rate of approximately 1 case per 1 million. Even in patients with predisposing conditions, CRC usually does not present until late adolescence or adulthood. Hereditary nonpolyposis colon cancer (HNPCC) is an autosomal dominant disorder, with germline mutations in DNA mismatch repair genes (MMR) causing DNA repair errors and microsatellite instability. Familial adenomatous polyposis (FAP) and attenuated FAP are autosomal disorders, with germline mutations in the APC gene. In addition to CRC, patients with HNPCC, FAP, and attenuated FAP are predisposed to a number of extracolonic cancers. Desmoid tumors can occur in patients with FAP, whereas patients with HNPCC have an increased risk for tumors involving the genitourinary tract, stomach, and small intestine. MYH-associated polyposis, Peutz-Jeghers syndrome, and juvenile polyposis also predispose to CRC.

Genetic testing is available, and screening for cancer in HNPCC and FAP should begin during childhood or adolescence. Likewise, genetic evaluation for these conditions should be pursued in young patients presenting with colon cancer, even when there is no history of predisposing genetic conditions.

Presenting symptoms include bloody stools or melena, abdominal pain, weight loss, and changes in bowel patterns. In many cases, signs are vague, often resulting in a delay in diagnosis, sometimes not until the disease has reached an advanced stage. The histologic subtype differs from that seen in adults, with the majority of pediatric tumors being either mucinous adenocarcinoma or signet ring cell carcinoma. Treatment consists of surgical resection when possible, with chemotherapy for unresectable tumors. Adequate lymph node removal should be performed at the time of surgical resection of primary tumor. Radiation therapy is useful in the treatment of rectal carcinomas.

Bibliography is available at Expert Consult.

506.5 Adrenal Tumors

Steven G. Waguespack

See Chapters 579 to 581.

Adrenocortical tumors (ACTs) arise from the outer adrenal cortex, whereas pheochromocytomas (PHEOs) derive from the catecholamine-producing chromaffin cells of the adrenal medulla. When catecholamine-producing tumors arise outside of the adrenal medulla, they are called paragangliomas (PGLs). The pathologic categorization of these tumors as benign or malignant does not always correlate well with the clinical behavior, making it difficult to differentiate malignant from benign disease based upon pathology alone. Hence, long-term follow-up is warranted. Because of the greater association with genetic disease, genetic counseling is also advised for all children diagnosed with an ACT or PHEO/PGL.

ACTs are very rare and tend to present before age 5 yr. They have a female predominance and are functional tumors in >90% of cases, primarily producing androgens and causing clinically apparent virilization. ACT may also present as an abdominal mass or pain. In children, ACTs are associated with Li-Fraumeni syndrome (germline inactivating mutations in the TP53 tumor-suppressor gene), Beckwith-Wiedemann syndrome, hemihyperplasia other than that seen as part of Beckwith-Wiedemann syndrome, and, very rarely, congenital adrenal hyperplasia. Other unusual causes of nodular adrenocortical disease, which usually present with Cushings syndrome, include the Carney complex and macronodular adrenal hyperplasia.

PHEOs/PGLs are rare tumors that are more likely to be bilateral, malignant, and secondary to a heritable tumor syndrome when diagnosed in children. von Hippel–Lindau disease is the most common genetic cause of PHEOs/PGLs in the pediatric population, followed by the familial PGL syndromes caused by mutations in the succinate dehydrogenase gene. MEN2 (types 2A and 2B) and neurofibromatosis type 1 are also in the differential diagnosis, but are mostly associated with a PHEO diagnosis during adulthood. Although hypertension is usually paroxysmal in adults with PHEO, hypertension is usually sustained in children, who may also lack the typical triad of headache, palpitations, and diaphoresis seen commonly in adults. The best screening test for PHEO/PGL is measurement of plasma and/or urine metanephrine levels.

The initial treatment of ACT and PHEO/PGL is surgery. Children with PHEO/PGL require preoperative medical management, typically with α and β blockade. First-line medical therapy for metastatic ACT includes mitotane and chemotherapy with cisplatin, etoposide, and doxorubicin. Metastatic PHEO/PGL has historically been treated with cyclophosphamide, vincristine, and dacarbazine. In cases of both ACT and PHEO/PGL, novel targeted agents are being studied for the treatment of advanced metastatic disease, which is typically nonresponsive to standard chemotherapeutic approaches. Endocrine therapy targeting hormonal overproduction may also be needed to palliate symptoms and improve quality of life.

Bibliography is available at Expert Consult.

506.6 Desmoplastic Small Round Cell Tumor

Nidale Tarek and Cynthia E. Herzog

Desmoplastic small round cell tumor is a very rare and aggressive mesenchymal tumor that occurs predominantly in adolescent and young adult males. It is associated with a diagnostic chromosomal translocation between the Ewing tumor gene and the Wilms tumor gene, t(11;22)(p13;q12). Patients typically present with a bulky abdominal mass, multiple peritoneal and omental implants, and symptoms of abdominal sarcomatosis, including pain, ascites, intestinal obstruction, hydronephrosis, and weight loss. Desmoplastic small roundcell tumor mainly involves the abdominal cavity but can spread to the lymph nodes, liver, lungs, and bones. Aggressive treatment with combination chemotherapy, debulking surgery, and whole abdominopelvic irradiation results almost universally in a poor outcome. Median survival ranges between 17 and 25 mo, and the 5 yr overall survival remains less than 20%. Alternative treatment options currently under investigation include hyperthermic intraperitoneal chemotherapy and radioimmunotherapy with monoclonal antibodies targeting different surface antigens on tumor cells.

Bibliography is available at Expert Consult.
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Bibliography

Chapter 507

Histiocytosis Syndromes of Childhood
Stephan Ladisch

The childhood histiocytoses constitute a diverse group of disorders, which, although individually rare, are frequently severe in their clinical expression. These disorders are grouped together because they have in common a prominent proliferation or accumulation of cells of the monocyte–macrophage system of bone marrow origin. Although these disorders sometimes are difficult to distinguish clinically, accurate diagnosis is essential nevertheless for facilitating progress in treatment. A systematic classification of the childhood histiocytoses is based on histopathologic findings (Table 507-1). A thorough, comprehensive evaluation of a biopsy specimen obtained at the time of diagnosis is essential. This evaluation includes studies such as electron microscopy and immunostaining that may require special sample processing.

CLASSIFICATION AND PATHOLOGY

Three classes of childhood histiocytosis are defined, based on histopathologic findings. The most well-known childhood histiocytosis, Langerhans cell histiocytosis (LCH), previously known as histiocytosis X, includes the clinical entities of eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. The normal Langerhans cell is an antigen-presenting cell of the skin. The hallmark of LCH in all forms is the presence of a clonal proliferation of cells of the monocyte lineage containing the characteristic Birbeck granule, a tennis racket–shaped bilamellar granule that, when seen in the cytosolic findings of a Langerhans cell. This is the monocyte–macrophage system of bone marrow origin. Although these disorders sometimes are difficult to distinguish clinically, accurate diagnosis is essential nevertheless for facilitating progress in treatment. A systematic classification of the childhood histiocytoses is based on histopathologic findings (Table 507-1). A thorough, comprehensive evaluation of a biopsy specimen obtained at the time of diagnosis is essential. This evaluation includes studies such as electron microscopy and immunostaining that may require special sample processing.

### Table 507-1 Classification of the Childhood Histiocytoses

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CELLULAR CHARACTERISTICS OF LESIONS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCH</td>
<td>Langerhans-like cells (CD1a-positive, CD207-positive) with Birbeck granules (LCH cells)</td>
<td>Local therapy for isolated lesions; chemotherapy for disseminated disease</td>
</tr>
<tr>
<td>HLH</td>
<td>Morphologically normal reactive macrophages with prominent erythrophagocytosis, and CD8-positive T cells</td>
<td>Chemotherapy; allogeneic bone marrow transplantation</td>
</tr>
<tr>
<td>Other</td>
<td>Characteristic vacuolated lesional histiocytes with foamy cytoplasm</td>
<td>None or excisional biopsy for localized disease; chemotherapy, radiotherapy for disseminated disease</td>
</tr>
<tr>
<td></td>
<td>Hemophagocytic histiocytes</td>
<td>None if localized; surgery for bulk reduction; chemotherapy if organ systems involvement</td>
</tr>
<tr>
<td></td>
<td>Neoplastic proliferation of cells with characteristics of monocytes/macrophages or their precursors</td>
<td>Antineoplastic chemotherapy, including anthracyclines</td>
</tr>
</tbody>
</table>

*Chediak-Higashi and Hermansky-Pudlik syndromes.
†Also called secondary hemophagocytic lymphohistiocytosis.
‡See Chapter 495.2.
FAB, French-American-British; LCH, Langerhans cell histiocytosis; HLH, hemophagocytic lymphohistiocytosis.
diseases are characterized by disseminated lesions that involve many organ systems. The lesions are characterized by infiltration of the involved organ with activated phagocytic macrophages and lymphocytes, in which the lymphocyte defects (cytolytic pathway) are considered to be the primary abnormality.

Noninfectious causes that may trigger secondary HLH include drugs (phenytoin, highly active antiretroviral therapy), bone marrow transplantation, chemotherapy, autoimmune diseases, inflammatory bowel disease, and immunodeficiency states (DiGeorge syndrome, Bruton agammaglobulinemia, severe combined immunodeficiency syndrome, chronic granulomatous disease, cancer).

These diseases together comprise HLH (Table 507-3 and Fig. 507-3). Multiple different steps in granule formation and release by cytotoxic T cells, when inhibited by genetic mutation, can result in primary HLH (Fig. 507-3, bottom). In an analogous way, a trigger (e.g., infection) can result in secondary HLH (Fig. 507-3, top).

The mixed cellular lesions of both LCH and HLH are increasingly believed to point to these being disorders of immune regulation resulting from either an unusual and unidentified antigenic stimulation and/or an abnormal and defective cellular immune response. Mutations in the perforin (PRF1) gene or the MUNC13-4 gene are the most common causes of defective function of the cytotoxic lymphocytes whose activity is inhibited in FHLH. Some cases of LCH demonstrate clonality of individual lesions. In LCH, a mutated form of the BRAF gene has been identified in many patients; its pathophysiologic significance is being

Table 507-2  Infections Associated with Hemophagocytic Syndrome

<table>
<thead>
<tr>
<th>VIRAL</th>
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<tbody>
<tr>
<td>Adenovirus</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Dengue virus</td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td></td>
</tr>
<tr>
<td>Enteroviruses</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex viruses (HSV1, HSV2)</td>
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</tr>
<tr>
<td>Human herpesviruses (HHV6, HHV8)</td>
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</tr>
<tr>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Influenza viruses</td>
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<tr>
<td>Parvovirus B19</td>
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<tr>
<td>Varicella-zoster virus</td>
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<tr>
<td>Hepatitis viruses</td>
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<tr>
<td>Measles</td>
<td></td>
</tr>
<tr>
<td>Parechovirus</td>
<td></td>
</tr>
</tbody>
</table>

| BACTERIAL              |                      |
| Babesia microti        |                      |
| Brucella abortus       |                      |
| Enteric Gram-negative rods |                  |
| Haemophilus influenzae |                      |
| Mycoplasma pneumoniae  |                      |
| Staphylococcus aureus  |                      |
| Streptococcus pneumoniae |                 |

| FUNGAL                 |                      |
| Candida albicans       |                      |
| Cryptococcus neoformans |                    |
| Histoplasma capsulatum |                      |
| Fusarium               |                      |

| MYCOBACTERIAL          |                      |
| Mycobacterium tuberculosis |                |

| RICKETTSIAL            |                      |
| Coxiella burnetii      |                      |
| Other rickettsial diseases |               |

| PARASITIC              |                      |
| Leishmania donovani    |                      |
| Plasmodium             |                      |

### Table 507-3  Classification of Primary HLH, Notable Clinical Findings, and Rapid Diagnostic Results

<table>
<thead>
<tr>
<th>HLH TYPE</th>
<th>DEFECTIVE GENE</th>
<th>FUNCTION</th>
<th>NOTABLE CLINICAL FINDINGS</th>
<th>RAPID DIAGNOSIS BY FLOW CYTOMETRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHLH-1</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>FHLH-2</td>
<td>Munc 13.4 PRF1</td>
<td>Pore formation</td>
<td>Increased incidence of CNS HLH, colitis, bleeding, hypogammaglobulinemia</td>
<td>Decreased/absent perforin expression</td>
</tr>
<tr>
<td>FHLH-3</td>
<td>Munc 13.4 STX11</td>
<td>Vesicle priming</td>
<td>Mild, recurrent HLH, colitis</td>
<td>Decreased CD107a expression</td>
</tr>
<tr>
<td>FHLH-4</td>
<td>Munc 13.4 STXBP2</td>
<td>Vesicle fusion</td>
<td>Partial albinism, bleeding tendency, and recurrent pyogenic infection</td>
<td>Decreased CD107a expression</td>
</tr>
<tr>
<td>FHLH-5</td>
<td>Munc 13.4 STXBP2</td>
<td>Vesicle fusion</td>
<td>Partial albinism, bleeding, hypogammaglobulinemia</td>
<td>Decreased CD107a expression</td>
</tr>
</tbody>
</table>

#### SYNDROMES

**Griscelli syndrome type II**
- RAB27A
  - Vesicle docking
  - Partial albinism and silvery-gray hair

**Chediak-Higashi syndrome**
- LYST
  - Vesicle trafficking
  - Partial albinism, bleeding tendency, and recurrent pyogenic infection

**Hermansky-Pudlak syndrome type II**
- AP3B1
  - Vesicle trafficking
  - Partial albinism, bleeding tendency, and immunodeficiency

**EPSTEIN-BARR VIRUS–DRIVEN**

**XLP-1**
- SAP/SH2D1A
  - Signaling in T, NK, and NK T cells
  - Hypogammaglobulinemia and lymphoma

**XLP-2/XIAP‡**
- BIRC4
  - Signaling pathways involving NF-kB
  - Mild, recurrent HLH and colitis

**IL-2–inducible T-cell kinase deficiency**
- CD27
  - Lymphocyte costimulatory molecule
  - AR, combined immunodeficiency

**CD27 deficiency**
- CD27
  - Absent CD27 expression on B cells

**XMEN**
- MAGT1
  - T-cell activation via T-cell receptor
  - Combined immunodeficiency, chronic viral infections, and lymphoma

*Light microscopy examination of a hair shaft shows a characteristic abnormal clumping of pigment.
†Light microscopy examination of peripheral blood smear shows giant granules in neutrophils and other leukocytes.
‡Defect is present in all tissues.


### Figure 507-3 Inborn errors in the cytotoxic activity of lymphocytes

**Top:** Schematic diagram of the immune mechanisms leading to the occurrence of a hemophagocytic syndrome. Following a viral infection, antigen-specific CD8+ T lymphocytes undergo massive expansion and activation and secrete high levels of interferon (IFN)-γ. The overwhelming activated effector cells induce excessive macrophage activation and pro-inflammatory cytokine production including tumor necrosis factor (TNF)-α and interleukin-6 (IL-6). Macrophages spontaneously phagocytose blood elements (here shown: platelets, red blood cells, and a polymorphonuclear cell). Activated lymphocytes and macrophages infiltrate various organs, resulting in massive tissue necrosis and organ failure. **Bottom:** The genetic defects causing hemophagocytic lymphohistiocytic syndrome (HLH) affect a precise step of the cytotoxic machinery, i.e. granule content, docking, priming, or fusion. Only the defects causing Griscelli syndrome (GS) and familial hemophagocytic lymphohistiocytosis (FHL) are shown. *(From Pachloupnik Schmid J, Cote M, Menager MM, et al: Inherited defects in cytotoxic lymphocyte activity. Immunol Rev 235:10-23, 2010.)*
assessed. The BRAF mutation suggests both that there is an autonomous proliferative element to the disease and that there may potentially be a new avenue for therapeutic approaches.

In addition to these two most common forms of childhood histiocytosis, LCH and HLH, a number of rarer diseases are also included under this rubric, because they have in common various abnormalities of these cell populations of myeloid origin. These other diseases include juvenile xanthogranuloma, in which the lesion histiocytes are vacuolated, with foamy cytoplasm, and the lesions evolve into mixed granulomas also containing eosinophils, lymphocytes, and other cells. Another rare histiocytosis is Rosai–Dorfman disease, also known as sinus histiocytosis with massive lymphadenopathy. Packing of sinusoids of the lymph nodes with histiocytes that are hemophagocytic characterizes Rosai-Dorfman disease, although extranodal involvement is not uncommon. The etiology of these 2 diseases is unknown.

Finally, there is also a group of unequivocal malignancies of cells of monocyte–macrophage lineage. By this definition, acute monocytic leukemia and true malignant histiocytosis are included among the class III histiocytoses (see Chapter 495). True neoplasms of Langerhans cells, while extremely rare, have been reported.

507.1 Langerhans Cell Histiocytosis

Stephan Ladisch

CLINICAL MANIFESTATIONS

LCH has an extremely variable presentation. The skeleton is involved in 80% of patients and may be the only affected site, especially in children older than 5 yr of age. Bone lesions may be single or multiple and are seen most commonly in the skull (Fig. 507-4). Other sites include the pelvis, femur, vertebra, maxilla, and mandible. They may be asymptomatic or associated with pain and local swelling. Involvement of the spine may result in collapse of the vertebral body, which can be seen radiographically, and may cause secondary compression of the spinal cord. In flat and long bones, osteolytic lesions with sharp borders occur and no evidence exists of reactive new bone formation until the lesions begin to heal. Lesions that involve weight-bearing long bones may result in pathologic fractures. Chronically draining, infected ears are commonly associated with destruction in the mastoid area. Bone destruction in the mandible and maxilla may result in teeth that, on radiographs, appear to be free floating. With response to therapy, healing may be complete.

Approximately 50% of patients experience skin involvement at some time during the course of disease, usually as a hard-to-treat scaly, papular, seborrheic dermatitis of the scalp, diaper, axillary, or posterior auricular regions. The lesions may spread to involve the back, palms, and soles. The exanthem may be petechial or hemorrhagic, even in the absence of thrombocytopenia. Localized or disseminated lymphadenopathy is present in approximately 33% of patients. Hepatosplenomegaly occurs in approximately 20% of patients. Various degrees of hepatic malfunction may occur, including jaundice and ascites.

Exophthalmos, when present, often is bilateral and is caused by retroorbital accumulation of granulomatous tissue. Gingival mucous membranes may be involved with infiltrative lesions that appear superficially like candidiasis. Otitis media is present in 30–40% of patients; deafness may follow destructive lesions of the middle ear. In 10–15% of patients, pulmonary infiltrates are found on radiography. The lesions may range from diffuse fibrosis and disseminated nodular infiltrates to diffuse cystic changes. Rarely, pneumonia may be a complication. If the lungs are severely involved, tachypnea and progressive respiratory failure may result.

Pituitary dysfunction or hypothalamic involvement may result in growth retardation. In addition, patients may have diabetes insipidus; patients suspected of having LCH should demonstrate the ability to concentrate their urine before going to the operating room for a biopsy. Rarely, panhypopituitarism may occur. Primary hypothyroidism as a result of thyroid gland infiltration also may occur.

Patients with multisystem disease who are affected more severely are those who have systemic manifestations, including fever, weight loss, malaise, irritability, and failure to thrive. These systemic manifestations will distinguish between patients who are at high risk of mortality (i.e., “risk organ”–positive patients), and those without, who are at low risk (i.e., “risk organ”–negative patients). The risk organs are liver, spleen, hematopoietic system, and lung. The distinction is important for deciding the intensity of the treatment approach and has been incorporated into standard treatment approaches for LCH, as delineated in the Histiocyte Society protocols. Bone marrow involvement may cause anemia and thrombocytopenia. Two uncommon but serious manifestations of LCH are hepatic involvement (leading to fibrosis and cirrhosis) and a peculiar central nervous system (CNS) involvement characterized by ataxia, dysarthria, and other neurologic symptoms. Hepatic involvement is associated with multisystem disease that is often already present at the time of diagnosis. In contrast, the CNS involvement, which is progressive and histopathologically characterized by gliosis, and for which no treatment is known, may be observed only many years after the initial diagnosis of LCH, which itself may have consisted only of mild bone disease. Neither of these manifestations evidences Langerhans cells or Birbeck granules, and both are suspected to be driven initially by cytokine abnormalities.

After tissue biopsy, which is diagnostic and is easiest to perform on skin or bone lesions, a thorough clinical and laboratory evaluation should be undertaken. This should include a series of studies in all patients (complete blood cell count, liver function tests, coagulation studies, skeletal survey, chest radiograph, and measurement of urine osmolality). In addition, detailed evaluation of any organ system that has been shown to be involved by physical examination or by these studies should be performed to establish the extent of disease before initiation of treatment.

TREATMENT AND PROGNOSIS

The clinical course of single-system disease (usually bone, lymph node, or skin) generally is benign, with a high chance of spontaneous remission. Therefore, treatment should be minimal and should be directed at arresting the progression of a bone lesion that could result in permanent damage before it resolves spontaneously. Curettage or, less often, steroid injection or low-dose local radiation therapy (5–6 Gy) may accomplish this goal. Multisystem disease, in contrast, should be treated with systemic multiagent chemotherapy. Several different regimens have been proposed, but central elements are the inclusion of vinblastine and steroids, both of which have been found to be very effective in treating LCH. Etoposide has more recently been excluded from standard treatment of multisystem LCH, while treatment of multisystem LCH includes therapy with multiple agents, designed to reduce mortality, reactivation of disease, and long-term consequences.
The response rate to therapy is now quite high, and mortality in severe LCH has been substantially reduced by multiagent chemotherapy, especially if the diagnosis is made accurately and expeditiously. The most recent treatment results, employing lengthened continuation therapy, show a greater than 85% survival rate in severe multisystem disease and a reduced rate of reactivation. Experimental therapies, suggested only for unresponsive disease (often in very young children with multisystem disease and organ dysfunction who have not responded to mulitagent initial treatment), include immunosuppressive therapy with cyclosporine/antithymocyte globulin and possibly imatinib, 2-chlorodeoxyadenosine, and stem cell transplantation. Late (fibrotic) complications, whether hepatic or pulmonary, are irreversible and require organ transplantation to be definitively treated. Current treatment approaches and experimental protocols for both LCH and HLH can be obtained at the website for the Histiocyte Society (http://www.histiocytesociety.org). An unresolved problem is treatment of the (usually late-onset) severe, progressive, and intractable LCH-associated neurodegenerative syndrome.

Bibliography is available at Expert Consult.

### 507.2 Hemophagocytic Lymphohistiocytosis

**Stephan Ladisch**

(See “Classification and Pathology” above.)

**CLINICAL MANIFESTATIONS**

The major forms of HLH, FHLF and secondary HLH, have a remarkably similar presentation consisting of a generalized disease process, most often with fever (90-100%), maculopapular and/or petechial rash (10-60%), weight loss, and irritability (see Tables 507-4 and 507-5). FHLH also is characterized by severe immunodeficiency. Children with FHLH generally are younger than 4 yr of age, and children with secondary HLH may present at an older age, but both forms are recognized as presenting at any age. **Physical examination** often reveals hepatosplenomegaly (70-100%), lymphadenopathy (20-50%), respiratory distress (40-90%), jaundice, and symptoms of CNS involvement (~50%) that are not unlike those of aseptic meningitis or acute demyelinating encephalomyelitis (see Chapter 600.3). MRI may demonstrate systemic T2-weighted/FLAIR hyperintensities in gray and white matter and in supratentorial and infratentorial regions. The cerebrospinal fluid pleocytosis (50-90%) in CNS involvement of FHLH is characterized by cells that are the same phagocytic macrophages found in the peripheral blood or bone marrow. The **diagnosis** can be made either on the basis of a molecular (genetic) defect (see “Treatment and Prognosis” below) or on the pathologic findings of hemophagocytosis in bone marrow biopsy, and is suggested by clinical findings of fever, splenomegaly, and associated laboratory findings (in both forms of HLH), including hypertriglyceridemia (80-100%), hypofibrinogenemia (65-85%), elevated levels of hepatic enzymes (30-90%), extremely elevated levels of circulating soluble interleukin-2 receptors released by the activated lymphocytes, very high levels of serum ferritin (often >10,000), and cytopenias (in ~90-100%; especially pancytopenia from hemophagocytosis in the marrow). Hemophagocytosis is not specific for HLH without other features. In addition, in some subgroups of HLH perforin assays may be normal. In the absence of genetic mutations, the diagnosis of HLH is based on a set of specific criteria formulated by the Histiocyte Society, the presence of 5 of 8 of which is considered diagnostic of HLH (see Table 507-4): fever, splenomegaly, cytopenia of 2 cell lines, hypertriglyceridemia or hypofibrinogenemia, hyperferritinemia, elevated soluble CD25 (interleukin-2 receptor), reduced or absent natural killer cells, and bone marrow, cerebrospinal fluid, or lymph node evidence of hemophagocytosis. There are patients with FHLH who have no known identifiable gene mutation. No absolute clinical or laboratory distinction can be made between FHLH and secondary HLH, although genetic markers for FHLH can complement a positive family history for other affected children.

In the absence of either (1) documented genetic defect coupled with defective NK cell cytotoxicity or (2) frank hemophagocytosis, great care should be taken in making the diagnosis of (secondary) HLH, with its implication of the use of cytotoxic chemotherapy. This is because the otherwise nonspecific criteria (indicative of inflammation) used to diagnose HLH can also be seen in diseases that are not always associated with hemophagocytosis (such as an overwhelming acute viral infection without T cell overactivation) in which the cytotoxic and immunosuppressive therapy used in treating HLH might be contraindicated.

**TREATMENT AND PROGNOSIS**

The diagnostic distinction between FHLH and secondary HLH sometimes can be based on the acute onset of secondary HLH in the presence of a documented infection. In this case, treatment of the underlying infection, coupled with supportive care, is critical. If the diagnosis is made in a setting of iatrogenic immunodeficiency, immunosuppressive treatment should be withdrawn and supportive care should be instituted along with specific therapy for underlying infection. When FHLH (gene mutations in perforin or Munc13-4 proteins) is diagnosed or is suspected together with no documentation of an infection, therapy currently includes etoposide, corticosteroids, and intrathecal methotrexate. It should be stressed that pancytopenia is not a

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**Table 507-4** Diagnostic Guidelines for Hemophagocytic Lymphohistiocytosis

The diagnosis of HLH is established by fulfilling one of the following two criteria:

1. A molecular diagnosis consistent with HLH (e.g., PRF mutations, SAP mutations)
2. Having 5 of the following 8 signs or symptoms:
   a. Fever
   b. Splenomegaly
   c. Cytopenia (affecting ≥2 cell lineages; hemoglobin ≤9 g/dL [or ≤10 g/dL for infants ≤4 wk of age], platelets ≤100,000/μL, neutrophils ≤1,000/μL)
   d. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL)
   e. Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
   f. Low or absent natural killer cell cytotoxicity
   g. Hyperferritinemia (≥500 ng/mL)
   h. Elevated soluble CD25 (interleukin-2Rα chain; ≥2,400 U/mL)

**Table 507-5** Spectrum of Diseases Characterized By Hemophagocytosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Primary HLH (see Table 507-3)</th>
<th>Infection-Associated HLH (see Table 507-3)</th>
<th>Malignancy-Associated HLH (see Table 507-2)</th>
<th>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY HLH (see Table 507-3)</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
<tr>
<td>HLH WITH IMMUNODEFICIENCY, AUTOINFLAMMATORY STATES</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
<tr>
<td>MACROPHAGE ACTIVATION SYNDROME (MAS) ASSOCIATED WITH AUTOIMMUNE DISEASE</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
<tr>
<td>Systemic-onset juvenile idiopathic arthritis</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
<td>Infection-Associated HLH (see Table 507-3)</td>
<td>Malignancy-Associated HLH (see Table 507-2)</td>
<td>Macrophage Activation Syndrome (MAS) Associated with Autoimmune Disease</td>
</tr>
</tbody>
</table>

Bibliography


contraindication to cytotoxic therapy in FHLH. Some recommend antithymocyte globulin and cyclosporine for maintenance therapy. Nevertheless, even with chemotherapy, FHLH remains ultimately fatal, often after a relapse of the disease. Allogeneic stem cell transplantation is effective in curing approximately 60% of patients with FHLH.

In contrast, in secondary HLH, it is critical that the underlying disease (e.g., infection, malignancy, or other) be identified and successfully treated. In many cases, such as when an infection can be documented and effectively treated, the prognosis may be excellent without any other specific treatment. However, when a treatable infection or other cause cannot be documented, which is the case in many patients presumed to have secondary HLH, the prognosis may be as poor as that of FHLH, and an identical chemotherapeutic approach, including etoposide, is recommended, even in the face of cytopenias. It is theorized that in both cases, by its cytotoxic effect on macrophages, etoposide interrupts cytokine production, the hemophagocytic process, and the accumulation of macrophages, all of which may contribute to the pathogenesis of infection-associated hemophagocytic syndrome. A broad spectrum of infectious agents, including viruses (e.g., cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), fungi, protozoa, and bacteria, may trigger secondary HLH, often in the setting of immunodeficiency (see Table 507-2). A thorough evaluation for infection should be undertaken in immunodeficient patients with hemophagocytosis. The same syndrome may be identified in conjunction with a rheumatologic disorder (e.g., systemic lupus erythematosus, Kawasaki disease) or a neoplasm (leukemia); in these cases, effective treatment of the underlying disease may cause resolution of the hemophagocytosis. In some patients, interferon and intravenous immunoglobulin have been effective.

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507.3 Other Histiocytoses

Stephan Ladisch

Other rare histiocytoses are appropriately named for their clinical presentation. Examples include xanthogranuloma in juvenile xanthogranuloma and striking lymphadenopathy in Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy). Juvenile xanthogranuloma may require systemic treatment with cytotoxic chemotherapy if the disease is disseminated. Rosai-Dorfman disease is usually not treated, although the massive lymphadenopathy may require treatment because of its tendency to cause physical obstruction. Acute monocytic leukemia and true malignant histiocytosis are included because they are unequivocal malignancies of the monocyte-macrophage lineage; they are discussed in Chapter 490.

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Bibliography


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The kidneys lie in the retroperitoneal space slightly above the level of the umbilicus. They range in length and weight, respectively, from approximately 6 cm and 24 g in a full-term newborn to ≥12 cm and 150 g in an adult. The kidney (Fig. 508-1) has an outer layer, the cortex, which contains the glomeruli, proximal and distal convoluted tubules, and collecting ducts; and an inner layer, the medulla, that contains the straight portions of the tubules, the loops of Henle, the vasa recta, and the terminal collecting ducts (Fig. 508-2).

The blood supply to each kidney usually consists of a main renal artery that arises from the aorta; multiple renal arteries can occur. The main artery divides into segmental branches within the medulla, becoming the interlobar arteries that pass through the medulla to the corticomedullary junction. At this point, the interlobar arteries branch to form the arcuate arteries, which run parallel to the surface of the kidney. Interlobular arteries originate from the arcuate arteries and give rise to the afferent arterioles of the glomeruli. Specialized muscle cells in the wall of the afferent arteriole and specialized distal tubular cells adjacent to the glomerulus (macula densa) form the juxtaglomerular apparatus that controls the secretion of renin. The afferent arteriole divides into the glomerular capillary network, which then recombines into the efferent arteriole (see Fig. 508-2). The juxamedullary efferent arterioles are larger than those in the outer cortex and provide the blood supply, as the vasa recta, to the tubules and medulla.

Each kidney contains approximately 1 million nephrons (each consisting of a glomerulus and associated tubules). There is a large distribution of "normal nephron number" in humans, with the mean ±2 SD ranging from 200,000 to 2 million nephrons/kidney. This variation can have major pathophysiologic significance as a risk factor for the later development of hypertension and progressive renal dysfunction. In humans, formation of nephrons is complete at 36-40 wk of gestation, but functional maturation with tubular growth and elongation continues during the 1st decade of life. Because new nephrons cannot be formed after birth, any disease that results in progressive loss of nephrons can lead to renal insufficiency. A decreased number of nephrons secondary to low birthweight, prematurity, and/or unknown genetic or environmental factors has been implicated as a significant risk factor for the development of primary hypertension and progressive renal dysfunction in adulthood. Low nephron number presumably results in hyperfiltration and eventual sclerosis of "overworked" nephron units.

The glomerular network of specialized capillaries serves as the filtering mechanism of the kidney. The glomerular capillaries are lined by endothelial cells (Fig. 508-3) and have very thin cytoplasm that contains many holes (fenestrations). The glomerular basement membrane (GBM) forms a continuous layer between the endothelial and mesangial cells on one side and the epithelial cells on the other. The membrane has 3 layers: a central electron-dense lamina densa; the lamina rara interna, which lies between the lamina densa and the endothelial cells; and the lamina rara externa, which lies between the lamina densa and the epithelial cells. The visceral epithelial cells cover the capillary and project cytoplasmic foot processes, which attach to the lamina rara externa. Between the foot processes are spaces or filtration slits. The
Kidney function is best measured as glomerular filtration rate (GFR). As the blood passes through the glomerular capillaries, the plasma is filtered through the glomerular capillary walls. The ultrafiltrate, which is cell free, contains all of the substances in plasma (electrolytes, glucose, phosphate, urea, creatinine, peptides, low-molecular-weight proteins) except proteins having a molecular weight of ≥68 kDa (such as albumin and globulins). The filtrate is collected in Bowman's space and enters the tubules. There its composition is modified by tightly regulated secretion and absorption of solute and fluid by the multiple tubular segments of the nephron and the ductal system, until it exits the kidney, via the ureter, as urine.

Glomerular filtration is the net result of opposing forces applied across the capillary wall. The force for ultrafiltration (glomerular capillary hydrostatic pressure) is a result of systemic arterial pressure, modified by the tone of the afferent and efferent arterioles. The major force opposing ultrafiltration is glomerular capillary oncotic pressure, created by the gradient between the high concentration of plasma proteins within the capillary and the almost protein-free ultrafiltrate in Bowman's space. Filtration may be modified by the rate of glomerular plasma flow, the hydrostatic pressure within Bowman's space, and/or the permeability of the glomerular capillary wall.

Although glomerular filtration begins at approximately the 6th wk of fetal life, kidney function is not necessary for normal intrauterine homeostasis because the placenta serves as the major fetal excretory organ. After birth, the GFR increases until renal growth ceases (by age ~18-20 yr in most people). To compare GFRs of children and adults, the GFR is standardized to the body surface area (1.73 m² of an “ideal” 70-kg adult. Even after correction for surface area, the GFR of a child does not approximate adult values until the 3rd yr of life (Fig. 508-5). The GFR may be estimated by measurement of the serum creatinine level. Creatinine is derived from muscle metabolism. Its production is relatively constant, and its excretion is primarily through glomerular filtration, although tubular secretion can become important as serum creatinine rises in renal insufficiency. In contrast to the concentration of blood urea nitrogen, which is affected by state of hydration and nitrogen balance, the serum creatinine level is primarily influenced by muscle mass and the level of glomerular function. The serum creatinine is of value only in estimating the GFR under steady-state conditions. A patient can have a normal serum creatinine level without effective renal function very shortly after the onset of acute renal failure with anuria. In this clinical setting, serum creatinine is an insensitive measure of decreased renal function because its level does not rise above normal until GFR falls by 30-40%.

The precise measurement of the GFR is accomplished by quantitatively measuring the clearance of a substance that is freely filtered across the capillary wall and is neither reabsorbed nor secreted by the tubules. The clearance (C) of such a substance is the volume of plasma that, when completely cleared of the contained substance, would yield an equal

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508.2 Glomerular Filtration

Cynthia G. Pan and Ellis D. Avner

Kidney function is best measured as glomerular filtration rate (GFR). As the blood passes through the glomerular capillaries, the plasma is filtered through the glomerular capillary walls. The ultrafiltrate, which is cell free, contains all of the substances in plasma (electrolytes, glucose, phosphate, urea, creatinine, peptides, low-molecular-weight proteins) except proteins having a molecular weight of ≥68 kDa (such as albumin and globulins). The filtrate is collected in Bowman's space and enters the tubules. There its composition is modified by tightly regulated secretion and absorption of solute and fluid by the multiple tubular segments of the nephron and the ductal system, until it exits the kidney, via the ureter, as urine.

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Bibliography

quantity of that substance excreted in the urine over a specified time. Renal clearance is calculated by the following formula:

\[
C_s = \frac{C}{V} \cdot \frac{1}{P}
\]

where \( C_s \) equals the clearance of substance \( s \), \( C \) represents the urinary concentration of \( s \), \( V \) represents the urinary flow rate, and \( P \) equals the plasma concentration of \( s \). To correct the clearance for individual body surface area, the formula is:

\[
\text{Corrected clearance (mL/min/1.73 m}^2) = \frac{C_s}{\text{Surface area (m}^2) \times 1.73}
\]

The GFR is optimally measured by the clearance of inulin, a fructose polymer having a molecular weight of approximately 5 kDa. Because the inulin clearance technique is cumbersome for use in clinical practice, the GFR is commonly estimated by the clearance of endogenous creatinine. Formulas that estimate creatinine clearance accurately in clinical settings have been useful tools in patient care. The “bedside” Schwartz formula is the most widely used pediatric formula and is based on the serum creatinine, patient height, and an empirical constant. The accuracy of this equation is further improved utilizing an additional endogenous marker, cystatin C, in addition to serum creatinine. Cystatin C is a 13.6 kDa protease inhibitor produced by nucleated cells. It continues to be tested as a clinical tool to completely replace creatinine-based formulas, as it has distinct advantages in estimating GFR. Unlike creatinine, cystatin C is unaffected by sex, height, muscle mass, bilirubin, or red blood cell hemolysis, and is not secreted by the renal tubules under any conditions.

The absence of plasma proteins larger than the size of albumin from the glomerular filtrate confirms the effectiveness of the glomerular capillary wall as a filtration barrier. Major factors restricting the filtration of these and other macromolecules include their size and their ionic charge. Morphologic studies suggest that the size-selective filtration barrier resides within the GBM. The endothelial cell, basement membrane, and epithelial cell of the glomerular capillary wall all possess strong negative ionic charges (heparan sulfate and glycoproteins containing sialic acid). Proteins in the blood have a relatively low isoelectric point, carry a net negative charge, and are repelled by the negatively charged sites of the glomerular capillary wall, thus restricting filtration.

Bibliography is available at Expert Consult.

### 508.3 Glomerular Diseases

**Cynthia G. Pan and Ellis D. Avner**

#### PATHOGENESIS

Glomerular injury may be a result of genetic, immunologic, perfusion, or coagulation disorders. Genetic disorders of the glomerulus may result from mutations in DNA exons encoding proteins located within the glomerulus, interstitium, or tubular epithelium; mutations in regulatory genes controlling DNA transcription; abnormal posttranscriptional modification of RNA transcripts; or abnormal posttranslational modification of proteins. Immunologic injury to the glomerulus results in glomerulonephritis, which is a generic term for several diseases, but more precisely a histopathologic term defining inflammation of the glomerular capillaries. Evidence that glomerulonephritis is caused by immunologic injury includes morphologic and immunopathologic similarities to experimental immune-mediated glomerulonephritis; the demonstration of immune reactants (immunoglobulin, complement) in glomeruli; abnormalities in serum complement; and the finding of autoantibodies (anti-GBM) in some of these diseases (Fig. 508-6). There appear to be 2 major mechanisms of immunologic injury: glomerular deposition of circulating antigen–antibody immune complexes and interaction of antibody with glomerular antigens in situ. In the latter circumstance, the antigen may be a normal component of the glomerulus (the noncollagenous domain [NC-1] of type IV

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![Figure 508-6 Cellular location of injury during glomerulonephritis](image-url)

*In health, solutes are filtered into the urinary space. The presence of abnormal amounts of protein or cells suggests glomerular pathology.*

(From Chadban SJ, Atkins RC: Glomerulonephritis, Lancet 365:1797–1806, 2005.)
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collagen, a putative antigen in human anti-GBM nephritis) or an antigen that has been deposited in the glomerulus.

In **immune complex–mediated** diseases, antibody is produced against, and combines with, a circulating antigen that is usually unrelated to the kidney (see Fig. 508-6). The immune complexes accumulate in GBMs and activate the complement system, leading to immune injury. Acute serum sickness in rabbits is produced by a single intravenous injection of bovine albumin. Within 1 wk after injection, a rabbit produces antibody against bovine albumin, and the antigen remains in the blood in high concentration. As antibody enters the circulation, it forms immune complexes with antigen. Although the amount of antibody in the circulation exceeds that of antibody (antigen excess), the complexes formed are small, remain soluble in the circulation, and are deposited in glomeruli. The processes involved in glomerular localization are not well understood but include characteristics of the complex (concentration, charge, size) and/or the glomerulus (mesangial trapping, negatively charged capillary wall); hydrodynamic forces; and the influence of various chemical mediators (angiogenesis II, prostaglandins).

With deposition of immune complexes in glomeruli, rabbits develop an acute proliferative glomerulonephritis. Immunofluorescence microscopy demonstrates granular (“lumpy-bumpy”) deposits containing immunoglobulin and complement in the glomerular capillary wall. Electron microscopic studies show these deposits to be on the epithelial side of the GBM and in the mesangium. For the next few days, as additional antibody enters the circulation, the antigen is ultimately removed from the circulation and the glomerulonephritis subsides.

An example of in situ antigen–antibody interaction is **anti–GBM antibody disease**, in which antibody reacts with antigen(s) of the GBM. Immunopathologic studies reveal linear deposition of immunoglobulin and complement along the GBM in Goodpasture syndrome (see Chapter 517) and certain types of rapidly progressive glomerulonephritis (see Chapter 516).

The inflammatory reaction that follows immunologic injury results from activation of 1 or more mediator pathways. The most important of these is the complement system, which has 2 initiating sequences: the classic pathway, which is activated by antigen–antibody immune complexes, and the alternative or properdin pathway, which is activated by polysaccharides and endotoxin. These pathways converge at C3; from that point on, the same sequence leads to lysis of cell membranes (see Chapter 133). The major noxious products of complement activation are produced after activation of C3 and include anaphylatoxin (which stimulates contractile proteins within vascular walls and increases vascular permeability) and chemotactic factors (C5a) that recruit neutrophils and perhaps macrophages to the site of complement activation, leading to consequent damage to vascular cells and basement membranes. Therapeutic agents to block the antibody production and components of the complement cascade are available and may provide additional tools to treat immune-mediated kidney injury (see Chapters 514 and 518).

The coagulation system may be activated **directly**, after endothelial cell injury that exposes the thrombogenic subendothelial layer (thereby initiating the coagulation cascade), or it may be activated **indirectly**, after complement activation. Consequently, fibrin is deposited within glomerular capillaries or within Bowman’s space as crescents. Activation of the coagulation cascade can also activate the kinin system, which produces additional chemotactic and anaphylatoxin–like factors.

**PATHOLOGY**

The glomerulus may be injured by several mechanisms, but it has only a limited number of histopathologic responses; different disease states can produce similar microscopic changes.

Proliferation of glomerular cells occurs in most forms of glomerulonephritis and may be generalized (involving all glomeruli) or focal (involving only some glomeruli and sparing others). Within a single glomerulus, proliferation may be diffuse (involving all parts of the glomerulus) or segmental (involving only 1 or more tufts, but not others). Proliferation commonly involves the endothelial and mesangial cells and is often associated with an increase in the mesangial matrix (see Fig. 508-6). Mesangial proliferation can result from deposition of immune complex within the mesangium. The resultant increase in cell size and number, and production of mesangial matrix, can increase glomerular size and narrow the lumens of glomerular capillaries, leading to renal insufficiency.

**Crescent formation** in Bowman’s space (capsule) is a result of proliferation of parietal epithelial cells and is often associated with clinical signs of renal dysfunction. Crescents develop in several forms of glomerulonephritis (termed rapidly progressive or crescentic; see Chapter 516) and are a characteristic response to deposition of fibrin in Bowman’s space. Newly formed crescents contain fibrin, the proliferating epithelial cells of Bowman’s space, basement membrane–like material produced by these cells, and macrophages that might have a role in the genesis of glomerular injury. Over the subsequent days to weeks, the crescent is invaded by connective tissue and becomes a fibroepithelial crescent. This process generally results in glomerular obsolescence and the clinical development of chronic renal failure. Crescent formation is often associated with glomerular cell death. The necrotic glomerulus has a characteristic eosinophilic appearance and usually contains nuclear remnants. Crescent formation is usually associated with generalized proliferation of the mesangial cells and with either immune complex or anti–GBM antibody deposition in the glomerular capillary wall.

Certain forms of acute glomerulonephritis show glomerular exudation of blood cells, including neutrophils, eosinophils, basophils, and mononuclear cells. The thickened appearance of GBM can result from a true increase in the width of the membrane (as seen in membranous glomerulopathy; see Chapter 512), from massive deposition of immune complexes that have staining characteristics similar to the membrane (as seen in systemic lupus erythematosus; see Chapter 514), or from the interposition of mesangial cells and matrix into the subendothelial space between the endothelial cells and the GBM. The last can give the basement membrane a split appearance, as seen in type I membranoproliferative glomerulonephritis (see Chapter 513) and other diseases.

**Sclerosis** refers to the presence of scar tissue within the glomerulus. Occasionally, pathologists use this term to refer to an increase in mesangial matrix.

**Tubulointerstitial fibrosis** is present in all patients who have glomerular disease and who develop progressive renal injury. This fibrosis is initiated by injury to either the glomeruli, which, if severe, may secondarily involve the tubules, or direct injury to the tubules themselves. Tubular injury recruits mononuclear cell infiltrate, which releases a variety of soluble factors that have fibrosis-promoting effects. Matrix proteins of the renal interstitium begin to accumulate, leading to eventual destruction of renal tubules and peritubular capillaries. The actual transformation of tubular epithelium to mesenchymal tissue can contribute to progressive tubulointerstitial fibrosis, a process termed epithelial-mesenchymal transformation.

**Bibliography** is available at Expert Consult.
Bibliography
Section 2

Conditions Particularly Associated with Hematuria

Table 509-1 Other Causes of Red Urine

<table>
<thead>
<tr>
<th>HEME POSITIVE</th>
<th>Other Causes of Red Urine</th>
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</thead>
<tbody>
<tr>
<td>HEME NEGATIVE</td>
<td></td>
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<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Dyes (Vegetable/Fruit)</td>
</tr>
<tr>
<td>Deferoxamine</td>
<td>Beets</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Blackberries</td>
</tr>
<tr>
<td>Iron sorbitol</td>
<td>Food and candy coloring</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Rhubarb</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Metabolites</td>
</tr>
<tr>
<td>Phenazopyridine</td>
<td>Homogentisic acid</td>
</tr>
<tr>
<td>Phenolphthalein</td>
<td>Melanin</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Methemoglobin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Porphyrin</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Tyrosinosis</td>
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<tr>
<td>Sulfasalazine</td>
<td>Uretas</td>
</tr>
</tbody>
</table>

Hematuria is defined as the presence of at least 5 red blood cells (RBCs) per microliter of urine and occurs with a prevalence of 0.5-2.0% among school-age children. Quantitative studies demonstrate that normal children can excrete more than 500,000 RBCs per 12 hr period; this increases with fever and/or exercise. In the clinical setting, qualitative estimates are provided by a urinary dipstick that uses a very sensitive peroxidase chemical reaction between hemoglobin (or myoglobin) and a colorimetric chemical indicator impregnated on the dipstick. Chem-strip (Boehringer Mannheim), a common commercially available dipstick, is capable of detecting 3-5 RBCs/µL of unspun urine. The presence of 10-50 RBCs/µL may suggest underlying pathology, but significant hematuria is generally considered as >50 RBCs/µL. False-negative results can occur in the presence of formalin (used as a urine preservative) or high urinary concentrations of ascorbic acid (i.e., in patients with vitamin C intake >2000 mg/day). False-positive results may be seen in a child with an alkaline urine (pH > 8), or more commonly following contamination with oxidizing agents such as hydrogen peroxide used to clean the perineum before obtaining a specimen. Microscopic analysis of 10-15 mL of freshly voided and centrifuged urine is essential in confirming the presence of RBCs suggested by >10 RBCs/µL, or a +1 positive urinary dipstick reading.

Red urine without RBCs is seen in a number of conditions (Table 509-1). Clinically significant heme-positive urine without RBCs may be caused by the presence of either hemoglobin or myoglobin. Hemoglobinuria without hematuria can occur in the presence of acute or chronic hemolysis. Myoglobinuria without hematuria occurs in the presence of rhabdomyolysis resulting from skeletal muscle injury and is generally associated with a 5-fold increase in the plasma concentration of creatinine kinase. Rhabdomyolysis is always clinically significant as it may lead to acute renal injury. It can occur secondary to viral myositis, crush injury, severe electrolyte abnormalities (hypertension, hypophosphatemia), hypotension, disseminated intravascular coagulation, toxins (drugs, venom), metabolic disorders of muscles, and prolonged seizures. Clinically innocuous heme-negative urine can appear red, cola colored, or burgundy, owing to ingestion of various foods (blackberries, beets), or dyes used in food and candy, whereas dark brown (or black) urine can result from various urinary metabolites.

Evaluation of the child with hematuria begins with a careful history, physical examination, and urinalysis. This information is used to determine the level of hematuria (upper vs lower urinary tract) and to determine the urgency of the evaluation based on symptomatology. Special consideration needs to be given to family history, identification of anatomic abnormalities and malformation syndromes, presence of gross hematuria, and manifestations of hypertension, edema, or heart failure.

Table 509-2 lists causes of hematuria. Upper urinary tract sources of hematuria originate within the nephron (glomerulus, tubular system, or interstitium). Lower urinary tract sources of hematuria originate from the pelvocaliceal system, ureter, bladder, or urethra. Hematuria from within the glomerulus is often associated with brown, cola- or tea-colored, or burgundy urine, proteinuria >100 mg/dL via dipstick, urinary microscopic findings of RBC casts, and deformed urinary RBCs (particularly acanthocytes). Hematuria originating within the tubular system may be associated with the presence of leukocytes or renal tubular casts. Lower urinary tract sources of hematuria may be associated with gross hematuria that is bright red or pink, terminal hematuria (gross hematuria occurring at the end of the urine stream), blood clots, normal urinary RBC morphology, and minimal proteinuria on dipstick (<100 mg/dL).

Patients with hematuria can present with a number of symptoms suggesting specific disorders. Tea- or cola-colored urine, facial or body edema, hypertension, and oliguria are classic symptoms of glomerulonephritis. Diseases commonly manifesting as glomerulonephritis include postinfectious glomerulonephritis, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis, Henoch-Schönlein purpura (HSP) nephritis, systemic lupus erythematosus (SLE) nephritis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyarteritis nodosa, Goodpasture syndrome, and hemolytic-uremic syndrome. A history of recent upper respiratory, skin, or gastrointestinal infection suggests postinfectious glomerulonephritis, hemolytic-uremic syndrome, or HSP nephritis. Rash and joint complaints suggest HSP or SLE nephritis.

Hematuria associated with glomerulonephritis is typically painless, but can be associated with flank pain when acute or unusually severe. Frequency, dysuria, and unexplained fevers suggest a urinary tract infection, whereas renal colic suggests nephrolithiasis. A flank mass can suggest hydronephrosis, renal cystic diseases, renal vein thrombosis, or tumor. Hematuria associated with headache, mental status changes, visual changes (diplopia), epistaxis, or heart failure suggests significant hypertension. Patients with hematuria and a history of trauma require immediate evaluation (see Chapter 72). Child abuse must always be suspected in the child presenting with unexplained perineal bruising and hematuria.

A careful family history is critical in the initial assessment of the child with hematuria given the numerous genetic causes of renal disorders. Hereditary glomerular diseases include hereditary nephritis (Alport syndrome), thin glomerular basement membrane disease, SLE nephritis, and IgA nephropathy (Berger disease). Other hereditary renal disorders with a hereditary component include both autosomal recessive and autosomal dominant polycystic kidney...
diseases, atypical hemolytic-uremic syndrome, urolithiasis, and sickle cell disease/trait.

A complete physical examination is critical to assess the cause of hematuria. Hypertension, edema, or signs of heart failure suggest acute glomerulonephritis. Several malformation syndromes are associated with renal disease including VATER (vertebral body anomalies, anal atresia, tracheoesophageal fistula, and renal dysplasia) syndrome. Abnormal masses may be caused by bladder distention in posterior urethral valves, hydronephrosis in ureteropelvic junction obstruction, polycystic kidney disease, or Wilms tumor. Hematuria seen in patients with neurologic or cutaneous abnormalities may be the result of a number of syndromic renal disorders including tuberous sclerosis, von Hippel-Lindau syndrome, and Zellweger (cerebrohepatorenal) syndrome. Anatomic abnormalities of the external genitalia may be associated with hematuria and/or renal disease.

Patients with gross hematuria present additional challenges because of the associated parental anxiety. The most common cause of gross hematuria is bacterial urinary tract infection. Urethrorrhagia, which is urethral bleeding in the absence of urine, is associated with dysuria and blood spots on underwear after voiding. This condition, which often occurs in prepubertal boys at intervals several months apart, has a benign self-limited course. Less than 10% of patients have evidence of glomerulonephritis. Recurrent episodes of gross hematuria suggest IgA nephropathy, Alport syndrome, or thin glomerular basement membrane disease. Dysuria and abdominal or flank pain are symptoms of idiopathic hypercalciuria, or urolithiasis. Table 509-3 lists common causes of gross hematuria; Figure 509-1 outlines a general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. Asymptomatic patients with isolated microscopic hematuria should not undergo extensive diagnostic evaluation, because such hematuria is often transient and benign.

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Table 509-2 Causes of Hematuria in Children

<table>
<thead>
<tr>
<th>UPPER URINARY TRACT DISEASE</th>
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<tbody>
<tr>
<td>Isolated renal disease</td>
</tr>
<tr>
<td>Immunoglobulin (Ig) A nephropathy (Berger disease)</td>
</tr>
<tr>
<td>Alport syndrome (hereditary nephritis)</td>
</tr>
<tr>
<td>Thin glomerular basement membrane nephropathy</td>
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<tr>
<td>Postinfectious GN (poststreptococcal GN)*</td>
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<tr>
<td>Membranous nephropathy</td>
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<tr>
<td>Membranoproliferative GN*</td>
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<tr>
<td>Rapidly progressive GN</td>
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<tr>
<td>Focal segmental glomerulosclerosis</td>
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<td>Anti-glomerular basement membrane disease</td>
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<td>Multisystem disease</td>
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<tr>
<td>Systemic lupus erythematosus nephritis*</td>
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<tr>
<td>Henoch-Schönlein purpura nephritis</td>
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<tr>
<td>Granulomatosis with polyangiitis (formerly Wegener granulomatosis)</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
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<td>Goodpasture syndrome</td>
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<tr>
<td>Hemolytic-uremic syndrome</td>
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<td>Sickle cell glomerulopathy</td>
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<td>Malformations (aneurysms, hemangiomas)</td>
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<td>Nutcracker syndrome</td>
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<td>Hemoglobinopathy (sickle cell trait/disease)</td>
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<thead>
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<tbody>
<tr>
<td>Inflammation (infectious and noninfectious)</td>
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<td>Cystitis</td>
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<tr>
<td>Urethritis</td>
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<tr>
<td>Urolithiasis</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Coagulopathy</td>
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<tr>
<td>Heavy exercise</td>
</tr>
<tr>
<td>Bladder tumor</td>
</tr>
<tr>
<td>Factitious syndrome, factitious syndrome by proxy*</td>
</tr>
</tbody>
</table>

*Denotes glomerulonephritides presenting with hypocomplementemia.
†Formerly Munchausen syndrome and Munchausen syndrome by proxy.
GN, glomerulonephritis.

Table 509-3 Common Causes of Gross Hematuria

<table>
<thead>
<tr>
<th>Urinary tract infection</th>
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<tbody>
<tr>
<td>Meatal stenosis</td>
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<td>Perineal irritation</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Urolithiasis</td>
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<tr>
<td>Hypercalciuria</td>
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<td>Glomerular</td>
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<td>Henoch-Schönlein purpura nephritis</td>
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<tr>
<td>IgA nephropathy</td>
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<tr>
<td>Alport syndrome (hereditary nephritis)</td>
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<tr>
<td>Thin glomerular basement membrane disease</td>
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<tr>
<td>Systemic lupus erythematosus nephritis</td>
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</tbody>
</table>

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Figure 509-1 Algorithm of the general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. ANA, antinuclear antibody; ASO, antistreptolysin O; BUN, blood urea nitrogen; C3/C4, complement; CBC, complete blood cell count; Cr, creatinine; RBC, red blood cell.
The child with completely asymptomatic isolated microscopic hematuria that persists on at least 3 urinalyses observed over a minimum of a 2 wk period poses a dilemma in regard to the degree of further diagnostic testing that should be performed. Significant disease of the urinary tract is uncommon with this clinical presentation. The initial evaluation of these children should include a urine culture followed by a spot urine for hypercalciuria with a calcium:creatinine ratio in culture-negative patients. In African-American patients, a sickle cell screen should be included. If these studies are normal, urinalysis of all first-degree relatives is indicated. Renal and bladder ultrasonography should be considered to rule out structural lesions such as tumor, cystic disease, hydronephrosis, or urolithiasis. Ultrasonography of the urinary tract is most informative in patients presenting with gross hematuria, abdominal pain, flank pain, or trauma. If these initial studies are normal, assessment of serum creatinine and electrolytes is recommended.

The finding of certain hematologic abnormalities can narrow the differential diagnosis. Anemia in this setting may be caused by hypervolemia with dilution associated with acute renal failure; decreased RBC production in chronic renal failure; hemolysis from hemolytic-uremic syndrome, a chronic hemolytic anemia, or SLE; blood loss from pulmonary hemorrhage, as seen in Goodpasture syndrome; or melena in patients with HSP or hemolytic-uremic syndrome. Inspection of the peripheral blood smear might reveal a microangiopathic process consistent with the hemolytic-uremic syndrome. The presence of autoantibodies in SLE can result in a positive Coombs test, the presence of antinuclear antibody, leukopenia, and multisystem disease. Thrombocytopenia can result from decreased platelet production (malignancies) or increased platelet consumption (SLE, idiopathic thrombocytopenic purpura, hemolytic-uremic syndrome, renal vein thrombosis, or congenital hepatic fibrosis with portal hypertension secondary to autosomal recessive polycystic kidney disease). Although urinary RBC morphology may be normal with lower tract bleeding and dysmorphic from glomerular bleeding, it is not sensitive enough to unequivocally delineate the site of hematuria. A bleeding diathesis is an unusual cause of hematuria. Coagulation studies are not routinely obtained unless personal or family history suggests a bleeding tendency.

A voiding cystourethrogram is only required in patients with a urinary tract infection, renal scarring, hydroureter, or pyelocaliectasis. Cystoscopy is an unnecessary and costly procedure in most pediatric patients with hematuria, and carries the associated risks of anesthesia. The diagnosis of “possible urethral stenosis” as an indication for cystoscopy should be viewed with a high degree of suspicion, because true urethral stenosis is quite rare. This procedure should be reserved for evaluating the rare child with a bladder mass noted on ultrasound, urethral abnormalities caused by trauma, posterior urethral valves, or tumor. The finding of unilateral gross hematuria localized by cystoscopy is rare, but it can indicate a vascular malformation or another anatomic abnormality. Children with persistent asymptomatic isolated hematuria and a completely normal evaluation should have their blood pressure and urine checked every 3 mo until the hematuria resolves. Referral to a pediatric nephrologist should be considered for patients with persistent asymptomatic hematuria greater than 1 yr duration and is recommended for patients with nephritis (glomerulonephritis, tubulointerstitial nephritis), hypertension, renal insufficiency, urolithiasis or nephrocalcinosis, or a family history of renal disease such as polycystic kidney disease or hereditary nephritis. Renal biopsy is indicated for some children with persistent microscopic hematuria, and most children with recurrent gross hematuria associated with decreased renal function, proteinuria, or hypertension.

*Bibliography is available at Expert Consult.*
Bibliography
Chapter 510
Isolated Glomerular Diseases with Recurrent Gross Hematuria
Cynthia G. Pan and Ellis D. Avner

Approximately 10% of children with gross hematuria have an acute or a chronic form of glomerulonephritis that may be associated with a systemic illness. The gross hematuria, which is usually characterized by brown or cola-colored urine, may be painless or associated with vague flank or abdominal pain. Presentation with gross hematuria is common within 1-2 days after the onset of an apparent viral upper respiratory tract infection in immunoglobulin (Ig) A nephropathy, and typically resolves within 5 days. This relatively short period contrasts to a latency period of 7-21 days occurring between the onset of a streptococcal pharyngitis or impetiginous skin infection and the development of poststreptococcal acute glomerulonephritis. Gross hematuria in these circumstances can last as long as 4-6 wk. Gross hematuria can also be seen in children with glomerular basement membrane (GBM) disorders such as hereditary nephritis (Alport syndrome [AS]) and thin GBM disease. These glomerular diseases can also manifest as microscopic hematuria and/or proteinuria without gross hematuria.

510.1 Immunoglobulin A Nephropathy (Berger Nephropathy)
Cynthia G. Pan and Ellis D. Avner

IgA nephropathy is the most common chronic glomerular disease in children. It is characterized by a predominance of IgA within mesangial glomerular deposits in the absence of systemic disease. Diagnosis requires renal biopsy, which is performed when clinical features warrant confirmation of the diagnosis or characterization of the histologic severity, which might affect therapeutic decisions.

PATHOLOGY AND PATHOLOGIC DIAGNOSIS
Focal and segmental mesangial proliferation and increased mesangial matrix are seen in the glomerulus (Fig. 510-1). Renal histology

Figure 510-1 Light microscopy of IgA nephropathy demonstrating segmental mesangial proliferation and increased matrix (×180).
CLINICAL AND LABORATORY MANIFESTATIONS

IgA nephropathy is seen more often in male than in female patients. Although there are rare cases of rapidly progressive forms of the disease, the clinical presentation of childhood IgA nephropathy is often benign in comparison to that of adults. IgA nephropathy is an uncommon cause of end-stage renal failure during childhood. A majority of children with IgA nephropathy in the United States and Europe present with gross hematuria, whereas microscopic hematuria and/or proteinuria is a more common presentation in Japan. Other presentations include acute nephritic syndrome, nephrotic syndrome, or a combined nephritic-nephrotic picture. Gross hematuria often occurs within 1-2 days of onset of an upper respiratory or gastrointestinal infection, in contrast to the longer latency period observed in acute postinfectious glomerulonephritis, and may be associated with loin pain. Proteinuria is often <1000 mg/24 hr in patients with asymptomatic microscopic hematuria. Mild to moderate hypertension is most often seen in patients with nephritic or nephrotic syndrome, but is rarely severe enough to result in hypertensive emergencies. Normal serum levels of C3 in IgA nephropathy help to distinguish this disorder from post-streptococcal glomerulonephritis. Serum IgA levels have no diagnostic value because they are elevated in only 15% of pediatric patients.

PROGNOSIS AND TREATMENT

Although IgA nephropathy does not lead to significant kidney damage in most children, progressive disease develops in 20-30% of patients 15-20 yr after disease onset. Therefore, most children with IgA nephropathy do not display progressive renal dysfunction until adulthood, prompting the need for careful long-term follow-up. Poor prognostic indicators at presentation or follow-up include persistent hypertension, diminished renal function, and significant, increasing, or prolonged proteinuria. A more severe prognosis is correlated with histologic evidence of diffuse mesangial proliferation, extensive glomerular crescents, glomerulosclerosis, and diffuse tubulointerstitial changes, including inflammation and fibrosis.

The primary treatment of IgA nephropathy is appropriate blood pressure control and management of significant proteinuria. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are effective in reducing proteinuria and retarding the rate of disease progression when used individually or in combination. Fish oil, which contains antiinflammatory omega-3 polyunsaturated fatty acids, may decrease the rate of disease progression in adults. If renin-angiotensin blockade proves ineffective and significant proteinuria persists, then addition of immunosuppressive therapy with corticosteroids is recommended. Corticosteroids reduce proteinuria and improve renal function in those patients with a glomerular filtration rate >60 mL/min/m². It remains unclear if the effects of glucocorticoids deter progression to end-stage renal failure to a degree to offset their significant side effects. To date, additional immunosuppression with cyclophosphamide or azathioprine has not appeared to be effective, but further randomized clinical trials are in progress. Tonsillectomy has been used as treatment for IgA nephropathy in many countries including Japan. Performing a tonsillectomy in the absence of significant tonsillitis in association with IgA nephropathy is currently not recommended until appropriate prospective, controlled trials have been performed and demonstrate efficacy. Patients with IgA nephropathy may undergo successful kidney transplantation. Although recurrent disease is frequent, allograft loss caused by IgA nephropathy occurs in only 15-30% of patients.

Bibliography is available at Expert Consult.

510.2 Alport Syndrome

Cynthia G. Pan and Ellis D. Avner

AS, or hereditary nephritis, is a genetically heterogeneous disease caused by mutations in the genes coding for type IV collagen, a major component of basement membranes. These genetic alterations are associated with marked variability in clinical presentation, natural history, and histologic abnormalities.

GENETICS

Approximately 85% of patients have X-linked inheritance caused by a mutation in the COL4A5 gene encoding the α5 chain of type IV collagen. Patients with a subtype of X-linked AS and diffuse leimyomatosus deposits demonstrate a contiguous mutation within the COL4A5 and COL4A6 genes that encodes the α5 and α6 chains, respectively, of type IV collagen. Autosomal recessive forms of AS are caused by mutations in the COLA43 and COLA44 genes on chromosome 2 encoding the α3 and α4 chains, respectively, of type IV collagen. An autosomal dominant form of AS linked to the COLA43-COLA44 gene locus occurs in 5% of cases.

PATHOLOGY

Kidney biopsy specimens during the 1st decade of life show few changes on light microscopy. Later, the glomeruli may develop mesangial proliferation and capillary wall thickening, leading to progressive glomerular sclerosis. Tubular atrophy, interstitial inflammation and fibrosis, and lipid-containing tubular or interstitial cells, called foam cells, develop as the disease progresses. Immunopathologic studies are usually nondiagnostic.

In most patients, electron microscopy reveals diffuse thickening, thinning, splitting, and layering of the glomerular and tubular basement membranes (Fig. 510-3). To confound diagnosis, ultrastructural analysis of the GBM in all genetic forms of AS may be completely normal, display nonspecific alterations, or demonstrate only uniform thinning.
**Bibliography**


PROGNOSIS AND TREATMENT

The risk of progressive renal dysfunction leading to end-stage renal disease (ESRD) is highest among hemizygotes and autosomal recessive homozygotes. ESRD occurs before age 30 yr in approximately 75% of hemizygotes with X-linked AS. The risk of ESRD in X-linked heterozygotes is 12% by age 40 yr and 30% by age 60 yr. Risk factors for progression are gross hematuria during childhood, nephrotic syndrome, and prominent GBM thickening. Intrafamilial variation in phenotypic expression results in significant differences in the age of ESRD among family members. No specific therapy is available to treat AS, although angiotensin-converting enzyme inhibitors (and possibly angiotensin-2 receptor inhibitors) can slow the rate of progression. Careful management of renal failure complications such as hypertension, anemia, and electrolyte imbalance is critical. Patients with ESRD are treated with dialysis and kidney transplantation (see Chapter 535). Approximately 5% of kidney transplantation recipients develop anti-GBM nephritis, which occurs primarily in males with X-linked AS who develop ESRD before age 30 yr.

Pharmacologic treatment of proteinuria with angiotensin-converting enzyme inhibition or angiotensin II receptor blockade has proven effective in other glomerular diseases and has also shown promise in AS. Screening of heterozygote carriers for significant renal disease in later adulthood and possible treatment of significant proteinuria is also recommended.

Bibliography is available at Expert Consult.

510.3 Thin Basement Membrane Disease

Cynthia G. Pan and Ellis D. Avner

Thin basement membrane disease (TBMD) is defined by the presence of persistent microscopic hematuria and isolated thinning of the GBM (and, occasionally, tubular basement membranes) on electron microscopy. Microscopic hematuria is often initially observed during childhood and may be intermittent. Episodic gross hematuria can also be present, particularly after a respiratory illness. Isolated hematuria in multiple family members without renal dysfunction is referred to as benign familial hematuria. Although most of these patients will not undergo renal biopsy, it is often presumed that the underlying pathology is TBMD. TBMD may be sporadic or transmitted as an autosomal dominant trait. Heterozygous mutations in the COL4A3 and COL4A4 genes, which encode the α3 and α4 chains of type IV collagen present in the GBM, result in TBMD. Rare cases of TBMD progress, and such patients develop significant proteinuria, hypertension, or renal insufficiency. Homozygous mutations in these same genes result in autosomal recessive AS. Therefore, in these rare cases, the absence of a positive family history for renal insufficiency or deafness would not necessarily predict a benign outcome. Consequently, monitoring patients with benign familial hematuria for progressive proteinuria, hypertension, or renal insufficiency is important through childhood and young adulthood.

Bibliography is available at Expert Consult.
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Bibliography
Chapter 511
Glomerulonephritis Associated with Infections

511.1 Acute Poststreptococcal Glomerulonephritis

Cynthia G. Pan and Ellis D. Avner

Group A β-hemolytic streptococcal infections are common in children and can lead to the postinfectious complication of acute glomerulonephritis (GN). Acute poststreptococcal glomerulonephritis (APSGN) is a classic example of the acute nephritic syndrome characterized by the sudden onset of gross hematuria, edema, hypertension, and renal insufficiency. It is one of the most common glomerular causes of gross
hematuria in children and is a major cause of morbidity in group A β-hemolytic streptococcal infections.

**ETIOLOGY AND EPIDEMIOLOGY**

APSGN follows infection of the throat or skin by certain “nephritogenic” strains of group A β-hemolytic streptococci. Epidemics and clusters of household (camps, military) cases occur throughout the world, and 97% of cases occur in less-developed countries. The overall incidence has decreased in industrialized nations, presumably as a result of improved hygienic conditions and the near eradication of streptococcal pyoderma. Poststreptococcal GN commonly follows streptococcal pharyngitis during cold-weather months and streptococcal skin infections or pyoderma during warm-weather months. Although epidemics of nephritis have been described in association with throat (serotypes M1, M4, M25, and some strains of M12) and skin (serotype M49) infections, this disease is most commonly sporadic.

**PATHOLOGY**

Glomeruli appear enlarged and relatively bloodless and show diffuse mesangial cell proliferation, with an increase in mesangial matrix (Fig. 511-1). Polymorphonuclear leukocyte infiltration is common in glomeruli during the early stage of the disease. Crescents and interstitial inflammation may be seen in severe cases, but these changes are not specific for poststreptococcal GN. Immunofluorescence microscopy reveals a pattern of “humpy-bumpy” deposits of immunoglobulin and complement on the glomerular basement membrane and in the mesangium. On electron microscopy, electron-dense deposits, or "humps," are observed on the epithelial side of the glomerular basement membrane (Fig. 511-2).

**PATHOGENESIS**

Morphologic studies and a depression in the serum complement (C3) level provide strong evidence that APSGN is mediated by immune complexes. Circulating immune complex formation with streptococcal antigens and subsequent glomerular deposition is thought less likely to be a pathogenic mechanism. Molecular mimicry whereby circulating antibodies elicited by streptococcal antigens react with normal glomerular antigens, in situ immune complex formation of antistreptococcal antibodies with glomerular deposited antigen, and complement activation by directly deposited streptococcal antigens continue to be considered as probable mechanisms of immunologic injury.

Group A streptococci possess M proteins, and nephritogenic strains are related to the M protein serotype. The search for the precise nephritogenic antigen(s) that cause disease suggests that streptococcal pyogenic exotoxin (SPE) B and nephritis-associated streptococcal plasmin receptor are promising candidates. Both have been identified in glomeruli of affected patients, and in 1 study, circulating antibodies to SPE B were found in all patients. Cross-reactivity of SPE B and other M proteins with various components of the glomerular basement membrane also give evidence for molecular mimicry.

**CLINICAL MANIFESTATIONS**

Poststreptococcal GN is most common in children ages 5-12 yr and uncommon before the age of 3 yr. The typical patient develops an acute nephritic syndrome 1-2 wk after an antecedent streptococcal pharyngitis or 3-6 wk after a streptococcal pyoderma. The history of a specific infection may be absent, because symptoms may have been mild or have resolved without patients receiving specific treatment or seeking the care of a medical provider.

The severity of kidney involvement varies from asymptomatic microscopic hematuria with normal renal function to gross hematuria with acute renal failure. Depending on the severity of renal involvement, patients can develop various degrees of edema, hypertension, and oliguria. Patients are at risk for developing encephalopathy and/or heart failure secondary to hypertension or hypervolemia. Hypertensive encephalopathy must be considered in patients with blurred vision, severe headaches, altered mental status, or new seizures. The effects of acute hypertension not only depend on the severity of hypertension but also the absolute change in comparison to the patient's baseline blood pressure and the rate at which it has risen. Respiratory distress, orthopnea, and cough may be symptoms of pulmonary edema and heart failure. Peripheral edema typically results from salt and water retention and is common; nephrotic syndrome develops in a minority (<5%) of childhood cases. Nonspecific symptoms such as malaise, lethargy, abdominal pain, or flank pain are common. Atypical presentations of APSGN include those with subclinical disease and those with severe symptoms but an absence of initial urinary abnormalities; in individuals who present with a purpuric rash, it is difficult to distinguish APSGN from Henoch-Schönlein purpura without a renal biopsy.

The acute phase generally resolves within 6-8 wk. Although urinary protein excretion and hypertension usually normalize by 4-6 wk after onset, persistent microscopic hematuria can persist for 1-2 yr after the initial presentation.

**DIAGNOSIS**

Urinalysis demonstrates red blood cells, often in association with red blood cell casts, proteinuria, and polymorphonuclear leukocytes. A
mild normochromic anemia may be present from hemodilution and low-grade hemolysis. The serum C3 level is significantly reduced in >90% of patients in the acute phase, and returns to normal 6-8 wk after onset. Although serum CH50 is commonly depressed, C4 is most often normal in APSGN, or only mildly depressed.

Confirmation of the diagnosis requires clear evidence of a prior streptococcal infection. A positive throat culture report might support the diagnosis or might represent the carrier state. A rising antibody titer to streptococcal antigen(s) confirms a recent streptococcal infection. The antistreptolysin O titer is commonly elevated after a pharyngeal infection but rarely increases after streptococcal skin infections. The best single antibody titer to document cutaneous streptococcal infection is the antideoxyribonuclease B level. If available, a positive streptozyme screen (which measures multiple antibodies to different streptococcal antigens) is a valuable diagnostic tool. Serologic evidence for streptococcal infections is more sensitive than the history of recent infections and far more sensitive than positive bacterial cultures obtained at the time of onset of acute nephritis.

Magnetic resonance imaging of the brain is indicated in patients with severe neurologic symptoms and can demonstrate posterior reversible encephalopathy syndrome in the parietooccipital areas on T2-weighted images. Chest x-ray is indicated in those with signs of heart failure or respiratory distress, or physical exam findings of a heart gallop, decreased breath sounds, rales, or hypoxemia.

The clinical diagnosis of poststreptococcal GN is quite likely in a child presenting with acute nephritic syndrome, evidence of recent streptococcal infection, and a low C3 level. However, it is important to consider other diagnoses such as systemic lupus erythematosus, endocarditis, membranoproliferative GN, and an acute exacerbation of chronic GN. Renal biopsy should be considered only in the presence of acute renal failure, nephrotic syndrome, absence of evidence of streptococcal infection, or normal complement levels. In addition, renal biopsy is considered when hematuria and proteinuria, diminished renal function, and/or a low C3 level persist more than 2 mo after onset. Persistent hypocomplementemia can indicate a chronic form of postinfectious GN or another disease such as membranoproliferative GN.

The differential diagnosis of poststreptococcal GN includes many of the causes of hematuria listed in Tables 509-2 and 511-1, and an algorithm to help with diagnosis is presented in Figure 511-3. Acute postinfectious GN can also follow other infections with coagulase-positive and coagulase-negative staphylococci, Streptococcus pneumoniae, and Gram-negative bacteria. The clinical course, histopathology, and laboratory features are similar to those described for APSGN. For some, the terms APSGN and acute postinfectious GN are used synonymously. Acute GN can occur after certain fungal, rickettsial, protozoan, parasitic, or viral diseases. Among the latter, influenza and parvovirus infections are particularly notable.

**COMPICATIONS**

Acute complications result from hypertension and acute renal dysfunction. Hypertension is seen in 60% of patients and is associated

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**Table 511-1** Summary of Primary Renal Diseases That Manifest as Acute Glomerulonephritis

<table>
<thead>
<tr>
<th>DISEASES</th>
<th>POSTSTREPTOCOCCAL GLOMERULONEPHRITIS</th>
<th>IgA NEPHROPATHY</th>
<th>GOODPASTURE SYNDROME</th>
<th>IDIOPATHIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL MANIFESTATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>All ages, mean 7 yr, 2:1 male</td>
<td>10-35 yr, 2:1 male</td>
<td>15-30 yr, 6:1 male</td>
<td>Adults, 2:1 male</td>
</tr>
<tr>
<td>Acute nephritic syndrome</td>
<td>90%</td>
<td>50%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Asymptomatic hematuria</td>
<td>Occasionally</td>
<td>50%</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>10-20%</td>
<td>Rare</td>
<td>Rare</td>
<td>10-20%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70%</td>
<td>30-50%</td>
<td>Rare</td>
<td>25%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>50% (transient)</td>
<td>Very rare</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Other</td>
<td>Latent period of 1-3 wk</td>
<td>Follows viral syndromes</td>
<td>Pulmonary hemorrhage; iron deficiency anemia</td>
<td>None</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>↑ ASO titers (70%)</td>
<td>↑ Serum IgA (50%)</td>
<td>Positive anti-GBM antibody</td>
<td>Positive ANCA in some</td>
</tr>
<tr>
<td>HLA-B12, D “EN” (9)*</td>
<td>HLA-Bw 35, DR4 (4)*</td>
<td>HLA-DR2 (16)*</td>
<td>None established</td>
<td></td>
</tr>
<tr>
<td>RENAL PATHOLOGY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light microscopy</td>
<td>Diffuse proliferation</td>
<td>Focal proliferation</td>
<td>Focal → diffuse proliferation with crescents</td>
<td>Crescentic GN</td>
</tr>
<tr>
<td>Immunochemistry</td>
<td>Granular IgG, C3</td>
<td>Diffuse mesangial IgA</td>
<td>Linear IgG, C3</td>
<td>No immune deposits</td>
</tr>
<tr>
<td>Electron microscopy</td>
<td>Subepithelial humps</td>
<td>Mesangial deposits</td>
<td>No deposits</td>
<td>No deposits</td>
</tr>
<tr>
<td>Prognosis</td>
<td>95% resolve spontaneously 5% RPGN or slowly progressive</td>
<td>Slow progression in 25-50%</td>
<td>75% stabilize or improve if treated early</td>
<td>75% stabilize or improve if treated early</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive</td>
<td>Uncertain (options include steroids, fish oil, and ACE inhibitors)</td>
<td>Plasma exchange, steroids, cyclophosphamide</td>
<td>Steroid pulse therapy</td>
</tr>
</tbody>
</table>

*Relative risk.

ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ASO, anti-streptolysin O; GBM, glomerular basement membrane; GN, glomerulonephritis; HLA, human leukocyte antigen; Ig, immunoglobulin; RPGN, idiopathic rapidly progressive glomerulonephritis.

with hypertensive encephalopathy in 10% of cases. Although the neurologic sequelae are often reversible with appropriate management, severe prolonged hypertension can lead to intracranial bleeding. Other potential complications include heart failure, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizures, and uremia. Acute renal failure can require treatment with dialysis.

**PREVENTION**

Early systemic antibiotic therapy for streptococcal throat and skin infections does not eliminate the risk of GN. Family members of patients with acute GN, especially young children, should be considered at risk and be cultured for group A β-hemolytic streptococci and treated if positive. Family pets, particularly dogs, have also been reported as carriers.

**TREATMENT**

Management is directed at treating the acute effects of renal insufficiency and hypertension (see Chapter 535.1). Although a 10 day course of systemic antibiotic therapy with penicillin is recommended to limit the spread of the nephritogenic organisms, antibiotic therapy does not affect the natural history of APSGN. This is unlike the GN seen in the context of ongoing or chronic infections, as noted in Chapter 511.2. Sodium restriction, diuresis (usually with intravenous furosemide), and pharmacotherapy with calcium channel antagonists, vasodilators, or angiotensin-converting enzyme inhibitors, are standard therapies used to treat hypertension.

**PROGNOSIS**

Complete recovery occurs in >95% of children with APSGN. Recurrences are extremely rare. Mortality in the acute stage can be avoided by appropriate management of acute renal failure, cardiac failure, and hypertension. Infrequently, the acute phase is severe and leads to glomerulosclerosis and chronic renal disease in <2% of affected children.

* Bibliography is available at Expert Consult.

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**511.2 Other Chronic Infections**
*Cynthia G. Pan and Ellis D. Avner*

GN is a recognized complication of various chronic infections. Classic examples include bacterial endocarditis caused by viridans streptococcus and other organisms, and ventriculobiliary shunts infected with *Staphylococcus epidermidis*. Other infections, observed less commonly in children than in adults, include hepatitis B virus, hepatitis C virus, syphilis, and candidiasis. Parasitic infections associated with glomerular disease include malaria, schistosomiasis, leishmaniasis, filariasis, hydatid disease, trypanosomiasis, and toxoplasmosis. In each condition, the infecting organism has low virulence and the host is chronically infected with foreign antigen. In the presence of high levels of circulating antigen, the host's antibody response leads to formation of immune complexes that deposit in the kidneys and initiate glomerular inflammation. Foreign antigens can also stimulate an autoimmune response through the production of antibodies that cross-react with such antigens incorrectly "recognized" as glomerular structural components.

The renal histopathology can resemble poststreptococcal GN, membranous GN, or membranoproliferative GN. The clinical manifestations are generally those of an acute nephritic or nephrotic syndrome. The serum C3 and CH50 complement levels are often decreased.

In HIV-associated nephropathy, direct viral infection of nephrons occurs because renal cells express a variety of lymphocyte chemokine receptors that are essential for and facilitate viral invasion. The renal expression of HIV infection is quite variable and includes an immune complex injury and a direct cytopathic effect. The classic histopathologic lesion of HIV-associated nephropathy is focal segmental glomerulosclerosis, but systemic lupus erythematosus-like glomerulonephritis, immunoglobulin A nephropathy, and membranous nephropathy have been reported. In the era of antiretroviral therapy, the decline in mortality has led to the increased recognition of renal disorders as an important complication to perinatally HIV-infected children.

Prompt eradication of any infection before severe glomerular injury occurs usually results in resolution of the GN. Progression to end-stage renal failure has been described but is uncommon. Spontaneous resolution of hepatitis B infection is common in children (30–50%) and results in remission of the glomerulopathy. Specific antivirals, interferon therapy, plasmapheresis, and immunosuppressive treatment have all been used successfully in adults with hepatitis C disease, but no controlled trials with any of these agents have been performed in pediatric patients.

* Bibliography is available at Expert Consult.
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Bibliography
Membranous nephropathy (MN), amongst the most common causes of nephrotic syndrome in adults, is a rare cause of nephrotic syndrome in children. MN is classified as the primary, idiopathic form, where there is isolated renal disease, or secondary MN, where nephropathy is associated with other identifiable systemic diseases or medications. In children, secondary MN is far more common than primary, idiopathic MN. The most common etiologies of secondary MN are systemic lupus erythematosus or chronic infections. Among the latter, chronic hepatic B infection and congenital syphilis are the best characterized and recognized causes of MN. Other chronic infections have also been associated with MN, including malaria, which is likely the most common cause of nephrotic syndrome worldwide. Certain medications, such as penicillamine and gold, or chronic factor replacement in patients with hemophilia can also cause MN. Rare causes associated with MN include tumors, such as neuroblastoma, or other idiopathic systemic diseases. Identification of secondary causes of MN is critical, because removal of the offending agent or treatment of the causative disease often leads to resolution of the associated nephropathy and improves patient outcome.

**PATHOLOGY**

Glomeruli have diffuse thickening of the glomerular basement membrane (GBM), without significant cell proliferative changes. Immunofluorescence and electron microscopy typically demonstrate granular deposits of immunoglobulin G and C3 located on the epithelial side of the GBM. The GBM thickening presumably results from the production of membrane-like material in response to deposition of immune complexes.

**PATHOGENESIS**

MN is believed to be caused by in situ immune complex formation. Therefore, antigens from the infectious agents or medications associated with secondary MN directly contribute to the pathogenesis of the renal disease. The causative antigen in idiopathic MN is not established, but the M-type phospholipase A2 receptor, present on normal podocytes, may be a target antigen in idiopathic MN. Antigen from this receptor is found in immune deposits extracted from glomeruli in patients with idiopathic MN. The majority of idiopathic MN patients have circulating antibody against this podocyte membrane antigen, as well as against several podocyte cytoplasmic antigens. Childhood MN may be associated with anticardiolipin bovine serum albumin antibodies. In addition, neutral endopeptidase antigen may be the antigen in neonatal onset MN.

**CLINICAL MANIFESTATIONS**

In children, MN is most common in the 2nd decade of life, but it can occur at any age, including infancy. The disease usually manifests as nephrotic syndrome and accounts for 2-6% of all cases of childhood nephrotic syndrome. Most patients also have microscopic hematuria and only rarely present with gross hematuria. Approximately 20% of children have hypertension at presentation. A subset of patients with MN present with a major venous thrombosis, commonly renal vein thrombosis. This well-known complication of nephrotic syndrome (see Chapter 527) is particularly common in patients with MN. Serum C3 and CH50 levels are normal, except in cases of systemic lupus erythematosus, where levels may be depressed (see Fig. 511-3 in Chapter 511).

**DIAGNOSIS**

MN might be suspected on clinical grounds, particularly in the setting of known risk factors for secondary forms of the disease. The diagnosis can only be established by renal biopsy. No serologic test is specific for MN, but finding an active carrier state for hepatitis B or congenital syphilis would make the diagnosis probable in the appropriate clinical setting. Common indications for renal biopsy leading to the diagnosis of MN include presentation with nephrotic syndrome in a child >10 yr or unexplained persistent hematuria with significant proteinuria.

**PROGNOSIS AND TREATMENT**

The clinical course of idiopathic membranous glomerulopathy is variable. Children presenting with asymptomatic, low-grade proteinuria can enter remission spontaneously. Retrospective reports of children 1-15 yr after diagnosis, treated with a variety of regimens, indicate that 20% progress to chronic renal failure, 40% continue with active disease, and 40% achieve complete remission. Although no controlled trials have been performed in children, immunosuppressive therapy with an extended course of prednisone can be effective in promoting complete resolution of symptoms. The addition of chlorambucil or cyclophosphamide appears to provide further benefit to those not responding to steroids alone. Rituximab has shown significant promise in adults and has been proposed by some as first line treatment but has yet to be studied in a randomized controlled trial in any age group. For those unresponsive to immunosuppression, or with mild clinical features, proteinuria can be reduced with angiotensin-converting enzyme inhibitors, and by analogy, probably angiotensin-II–receptor blockers.

*Bibliography is available at Expert Consult.*
Bibliography
Membranoproliferative glomerulonephritis (MPGN), also known as mesangiocapillary glomerulonephritis, most commonly occurs in children or young adults. MPGN can be classified into primary (idiopathic) and secondary forms of glomerular disease. Secondary forms of MPGN are most commonly associated with subacute and chronic infection, including hepatitis B and C, syphilis, subacute bacterial endocarditis, and infected shunts, especially ventriculoatrial shunts (shunt nephritis). MPGN can also be one of the glomerular lesions seen in lupus nephritis (see Chapter 514).

**PATHOLOGY**

Primary MPGN is defined by the histologic pattern of glomeruli as seen by light, immunofluorescence, and electron microscopy. Two subtypes have been defined on histologic criteria and are associated with different clinical phenotypes. **Type I MPGN** is most common. Glomeruli have an accentuated lobular pattern from diffuse mesangial expansion, endocapillary proliferation, and an increase in mesangial cells and matrix. The glomerular capillary walls are thickened, often with splitting from interposition of the mesangium. Crescents, if present, indicate a poor prognosis. Immunofluorescence microscopy reveals C3 and lesser amounts of immunoglobulin in the mesangium and along the peripheral capillary walls in a lobular pattern. Electron
microscopy confirms numerous deposits in the mesangial and subendothelial regions.

Far less common is type II MPGN, also called dense deposit disease, which has similar light microscopic findings as type I MPGN. Differentiation from type I disease is by immunofluorescence and electron microscopy. In type II disease, C3 immunofluorescence typically is prominent, without concomitant immunoglobulin. By electron microscopy, the lamina densa in the glomerular basement membrane undergoes a very dense transformation, without evident immune complex deposits.

C3 glomerulonephritis (C3GN) is a related but separate diagnostic category. By light and electron microscopy C3GN usually has features indistinguishable from classical MPGN. Immunofluorescence studies distinguish between the two, with C3GN having only C3 deposition and MPGN having both C3 and immunoglobulin fluorescence.

PATHOGENESIS

Although the histology of type I MPGN produced by primary and secondary forms is indistinguishable, it appears that type I disease occurs when circulating immune complexes become trapped in the glomerular subendothelial space, which then causes injury, resulting in the characteristic proliferative response and mesangial expansion. Further evidence confirming this pathway to glomerular injury is the finding of complement activation through the classical pathway in as many as 50% of affected patients.

Type II MPGN appears not to be mediated by immune complexes. The pathogenesis of the disease is not known, but the characteristic finding of severely depressed serum complement levels suggests that deranged complement regulation might play a major role in the disease. A typical finding is markedly depressed serum C3 complement levels, with normal levels of other complement components. In many patients with type II MPGN, C3 nephritic factor (anti–C3 convertase antibody) is present. This factor activates the alternative complement pathway. In unusual cases, patients with type II MPGN demonstrate an associated systemic disease called partial lipodystrophy, where there is diffuse loss of adipose tissue and decreased complement in the presence of C3 nephritic factor. Correlation between the presence of C3 nephritic factor, complement levels, and disease presence or severity is not strong, indicating that the complement abnormalities alone are not sufficient to cause the disease.

Type II MPGN (dense deposit disease) is considered part of the broader spectrum of C3GN. The latter, as defined above pathologically, appears to be caused by primary dysregulation of the alternative or terminal cascade complement pathways.

CLINICAL MANIFESTATIONS

MPGN is most common in the 2nd decade of life. Systemic features may provide clues to which type of MPGN may be present, but the two histologic types of idiopathic MPGN are indistinguishable in terms of their renal manifestations. Patients present in equal proportions with nephrotic syndrome, acute nephritic syndrome (hematuria, hypertension, and some level of renal insufficiency), or persistent asymptomatic microscopic hematuria and proteinuria. Serum C3 complement levels are low in the majority of cases (see Fig. 511-3 in Chapter 511).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes all forms of acute and chronic glomerulonephritis, including idiopathic and secondary forms, along with postinfectious glomerulonephritis. Postinfectious glomerulonephritis, far more common than MPGN, usually does not have nephrotic features but typically has hematuria, hypertension, renal insufficiency, and transiently low C3 complement, all features that may be seen with MPGN or C3GN. In contrast to MPGN and C3GN, where C3 levels usually remain persistently low, C3 returns to normal within 2 mo after onset of postinfectious glomerulonephritis (see Chapter 511.3). The diagnosis of MPGN is made by renal biopsy. Indications for biopsy include nephrotic syndrome in an older child, significant proteinuria with microscopic hematuria, and hypocomplementemia lasting >2 mo in a child with acute nephritis. If C3 but no immunoglobulin deposition is found in glomeruli with MPGN, genetic testing and functional assays to define defects of complement cascade regulation should be pursued.

PROGNOSIS AND TREATMENT

It is important to determine whether MPGN is idiopathic or secondary to a systemic disease, particularly lupus or chronic infection, because treatment of the causative disease can result in resolution of MPGN. Untreated, idiopathic MPGN, regardless of type, has a poor prognosis. By 10 yr following onset, 50% of patients with MPGN have progressed to end-stage renal disease. By 20 yr following onset, up to 90% have lost renal function. Those with nephrotic syndrome at the time of presentation progress to renal failure more rapidly. No definitive therapy exists, but several reports, including a randomized controlled trial, indicate that extended courses of alternate-day prednisone (for years) provide benefit. Some patients treated with steroids enter a complete clinical remission of their disease, but many have ongoing disease activity. Nevertheless, an extended course of prednisone is associated with significant preservation of renal function when compared with patients receiving no such treatment.

The prognosis of C3GN, separate from dense deposit disease (considered a part of C3GN by some) and other forms of classically defined MPGN is as yet hard to define, since reports of outcome of such patients previously had been grouped in studies of all forms of MPGN (types I and II, and even a poorly characterized type III form not considered above). The apparent pathophysiology of C3GN promises that treatments targeting the interruption of complement activation pathways, such as complement factor H replacement or shutting down the terminal complement cascade by blocking C5 activation with eculizumab (anti–C5 antibody), could be beneficial in preventing progression of renal disease.

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Chapter 514
Glomerulonephritis Associated with Systemic Lupus Erythematosus
Cynthia G. Pan and Ellis D. Avner

Systemic lupus erythematosus (SLE) is characterized by fever, weight loss, dermatitis, hematologic abnormalities, arthritis, and involvement of the heart, lungs, central nervous system, and kidneys (see Chapter 158). Glomerulonephritis is the most important cause of morbidity and mortality in SLE. Renal disease in childhood SLE is present in up to 80% of patients and is more active than that seen in adults. Occasionally, renal disease is the only presenting clinical manifestation.

PATHOGENESIS AND PATHOLOGY
The clinical manifestations of SLE are mediated by immune complexes. Autoantibodies are directed predominantly at nuclear antigens which act as immunogens. Binding of autoantibodies to glomerular components rather than the passive “trapping” of circulating immune complexes is central to the development of glomerulonephritis. Other pathogenic mechanisms include alterations in innate immunity that
result in amplification of inflammation. Deficiency of the complement component C1q is rare but is the strongest single genetic risk for SLE.

Kidney biopsy and evaluation of renal histopathology remain the gold standard for establishing the diagnosis of SLE nephritis and determining specific therapeutic regimens. The World Health Organization (WHO) classification of lupus nephritis is based on a combination of features including light microscopy, immunofluorescence, and electron microscopy. In patients with WHO class I nephritis (minimal mesangial lupus nephritis), no histologic abnormalities are detected on light microscopy but mesangial immune deposits are present on immunofluorescence or electron microscopy. In WHO class II nephritis (mesangial proliferative nephritis), light microscopy shows both mesangial hypercellularity and increased matrix along with mesangial deposits containing immunoglobulin and complement.

WHO class III nephritis and WHO class IV nephritis are related lesions characterized by both mesangial and endocapillary lesions. Class III nephritis is defined by <50% glomeruli with involvement and class IV has ≥50% glomerular involvement. Immune deposits are present in both the mesangium and subendothelial areas. A subclassification scheme helps grade severity of the proliferative lesion based on whether the glomerular lesions are segmental (<50% glomerular tuft involved) or global (≥50% glomerular tuft involved). The WHO classification scheme also delineates whether there is a predominance of chronic disease versus active disease. Chronic injury results in glomerular sclerosis and is felt to be the consequence of significant proliferative disease seen in classes III and IV. Other signs of active disease include capillary walls that are thickened secondary to subendothelial deposits (creating the wire-loop lesion), necrosis, and crescent formation. WHO class IV nephritis is associated with poorer outcomes but can be successfully treated with aggressive immunosuppressive therapy.

WHO class V nephritis (membranous lupus nephritis) is less commonly seen as an isolated lesion and resembles idiopathic membranous nephropathy with subepithelial immune deposits. This lesion is often seen in combination with class III or IV proliferative nephritis, and if the membranous lesion is present in >50% glomeruli, both classes are noted in designation. This classification scheme also identifies cases with combinations of mixed classes III, IV, and V lesions, directing appropriate treatment for such patients. Another classification scheme by both the International Society of Nephrology and the Renal Pathology Society differs mainly in its subclassification of class IV lesions into diffuse global and diffuse segmental lesions (Table 514–1). The value of utilizing this classification scheme, and more importantly, its impact on therapy and the results of clinical trials is unknown at this time.

Transformation of the histologic lesions of lupus nephritis from one class to another is common. This is more likely to occur among inadequately treated patients and usually results in progression to a more severe histologic lesion.

### CLINICAL MANIFESTATIONS

The majority of children with SLE are adolescent females. Lupus nephritis affects most pediatric patients, and although commonly presenting within the first year of diagnosis, may occur at any time during the course of the disease. Ethnicity and socioeconomic factors strongly predict the development of lupus nephritis in adults with SLE but not in children. The clinical findings in patients having milder forms of lupus nephritis (all classes I-II, some class III) include hematuria, normal renal function, and proteinuria < 1 g/24 hr. Some patients with class III and all patients with class IV nephritis have hematuria and proteinuria, hypertension, reduced renal function, nephrotic syndrome, or acute renal failure. The urinalysis may be normal on rare occasions in patients with proliferative lupus nephritis. Patients with class V nephritis commonly present with nephrotic syndrome.

### DIAGNOSIS

The diagnosis of SLE is confirmed by the detection of circulating antinuclear antibodies and by demonstrating antibodies that react with native double-stranded DNA. In most patients with active disease, C3 and C4 levels are depressed. In view of the lack of a clear correlation between the clinical manifestations and the severity of the renal involvement, renal biopsy should be performed in all patients with SLE. Histopathologic findings are used to determine the selection of specific immunosuppressive therapies.

### TREATMENT

Children with SLE should be treated by pediatric specialists in medical centers where medical and psychologic support can be provided for patients and their families. The goal of immunosuppressive therapy in lupus nephritis is to produce both a clinical remission, defined as normalization of renal function and proteinuria, and a serologic remission, defined as normalization of anti-DNA antibody, C3, and C4 levels. Therapy is initiated in all patients with proteinuria at a dose of 1-2 mg/kg/day in divided doses followed by a slow steroid taper over 4-6 mo beginning 4-6 wk after achieving a serologic remission. For patients with severe forms of nephritis (WHO classes III and IV), induction therapy consists of 6 consecutive monthly intravenous infusions of cyclophosphamide at a dose of 500-1,000 mg/m<sup>2</sup>. Pulse intravenous methylprednisolone (1000 mg/m<sup>2</sup>) is also used in addition to oral corticosteroids. In adult clinical trials, mycophenolate mofetil was shown to be equally efficacious for induction therapy and may be considered for use in children using 600 mg/m<sup>2</sup>/dose twice daily. Maintenance therapy previously consisted of additional Cytoxan infusions every 3 mo for 18 mo, which reduced the risk of progressive renal dysfunction. Maintenance therapy using mycophenolate mofetil or azathioprine may be as efficacious as intravenous cyclophosphamide and result in less-serious side effects, such as infections, hair loss, hemorrhagic cystitis, and gonadal failure. Mycophenolate mofetil is particularly more efficacious than cyclophosphamide in African-Americans. Azathioprine, at a single daily dose of 1.5-2.0 mg/kg, may be used as a steroid-sparing agent in patients with WHO class I or II

### Table 514–1

<table>
<thead>
<tr>
<th>CLASS</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Minimal mesangial LN</td>
<td>No renal findings</td>
</tr>
<tr>
<td>II. Mesangial proliferative LN</td>
<td>Mild clinical renal disease; minimally active urinary sediment; mild to moderate proteinuria (never nephrotic) but may have active serology</td>
</tr>
<tr>
<td>III. Focal proliferative LN &lt;50% glomeruli involved A. Active</td>
<td>More active sediment changes; often active serology; increased proteinuria (approximately 25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment, chronic do not</td>
</tr>
<tr>
<td>A/C. Active and chronic C. Chronic</td>
<td></td>
</tr>
<tr>
<td>IV. Diffuse proliferative LN (≥50% glomeruli involved); all may be with segmental or global involvement (S or G) A. Active</td>
<td>Most severe renal involvement with active sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), often reduced glomerular filtration rate; serology very active. Active lesions require treatment</td>
</tr>
<tr>
<td>A/C. Active and chronic C. Chronic</td>
<td></td>
</tr>
<tr>
<td>V. Membranous LN</td>
<td>Significant proteinuria (often nephrotic) with less active lupus serology</td>
</tr>
<tr>
<td>V. Membranous LN</td>
<td></td>
</tr>
<tr>
<td>V. Membranous LN</td>
<td></td>
</tr>
<tr>
<td>VI. Advanced sclerosing LN</td>
<td>More than 90% glomerulosclerosis; no treatment prevents renal failure</td>
</tr>
</tbody>
</table>

LN, lupus nephritis.

lupus nephritis. Rituximab, a chimeric monoclonal antibody specific for human CD20, is ineffective for induction therapy for diffuse proliferative disease but may be considered in cases where resistance to conventional treatment is demonstrated. Plasmapheresis is ineffective in lupus nephritis unless there is accompanying thrombotic thrombocytopenic purpura or antineutrophilic cytoplasmic antibody–associated disease. New therapies include belimumab, a fully humanized monoclonal antibody against a type II transmembrane protein that functions in the normal survival and differentiation of B cells, which is FDA-approved for use in SLE. Its role in lupus nephritis, either in combination with current therapies or to replace them, requires extensive further study.

Hydrochloroquine is prescribed in most patients with SLE for extra-renal manifestations, but is thought to have a beneficial effect in maintaining remission in lupus nephritis. It is a rational choice given its low side effect profile. Use of antihypertensive drugs to aggressively treat hypertension as well as the specific use of drugs that block the renin–angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers) to reduce proteinuria are also important therapies that appear to decrease long-term progression of renal disease.

**PROGNOSIS**
Overall, renal survival (defined as chronic kidney disease without the need for end-stage renal disease therapy) is seen in 80% of patients 10 yr after the diagnosis of SLE nephritis. Patients with diffuse proliferative WHO class IV lupus nephritis exhibit the highest risk for progression to end-stage renal disease. Concerns regarding the side effects of chronic immunosuppressive therapy and the risk of recurrent disease are lifelong. Close monitoring for relapse of disease is critical to ensure maximally successful renal outcomes. Special care must be taken to minimize the risks of infection, osteoporosis, obesity, poor growth, hypertension, and diabetes mellitus associated with chronic corticosteroid therapy. Patients require counseling regarding the risk of malignancy or infertility, which may be increased in those receiving a cumulative dose of >20 g of cyclophosphamide or other immunosuppressant therapies.

*Bibliography is available at Expert Consult.*
Bibliography


Henoch-Schönlein purpura (HSP) is the most common small vessel vasculitis in childhood. It is characterized by a purpuric rash and commonly accompanied by arthritis and abdominal pain (see Chapter 167.1). Approximately 50% of patients with HSP develop renal manifestations, which vary from asymptomatic microscopic hematuria to severe, progressive glomerulonephritis.

PATHOGENESIS AND PATHOLOGY

The pathogenesis of HSP nephritis appears to be mediated by the deposition of polymeric immunoglobulin A (IgA) in glomeruli. This is analogous to the same type of IgA deposits seen in systemic small vessels, primarily those of the skin and intestine. The glomerular findings can be indistinguishable from those of IgA nephropathy (see Chapter 510.1). IgA deposits are present by immunofluorescence, and a broad spectrum of glomerular lesions that can range from mild proliferation to necrotic and crescentic changes can be seen.

CLINICAL AND LABORATORY MANIFESTATIONS

The nephritis associated with HSP usually follows onset of the rash, often presenting weeks or even months after the initial presentation of the disease. Nephritis can be manifest at initial presentation, but only rarely before onset of the rash. Patients at presentation rarely display a severe combined acute nephritic and nephrotic picture (hematuria, hypertension, renal insufficiency, significant proteinuria, and nephrotic syndrome). Most patients have only mild renal manifestations, principally isolated microscopic hematuria without significant proteinuria. Initial mild renal involvement can occasionally progress to more severe nephritis despite resolution of all other features of HSP. The severity of the systemic manifestations does not correlate with the severity of the nephritis. Most patients who develop nephritis have urinary abnormalities by 1 mo, and nearly all have abnormalities by 3 mo after onset of HSP. Therefore, a urinalysis should be performed weekly in patients with HSP during the period of active clinical disease. Thereafter, a urinalysis should be performed once a month for up to 6 mo. If all urinalyses are normal during this follow-up interval, nephritis is unlikely to develop. If proteinuria, renal insufficiency, or hypertension develops along with hematuria, consultation with a pediatric nephrologist is indicated.

PROGNOSIS AND TREATMENT

The prognosis of HSP nephritis for most patients is excellent. Spontaneous and complete resolution of the nephritis typically occurs in the majority of patients with mild initial manifestations (isolated hematuria with insignificant proteinuria). However, such patients uncommonly can progress to severe renal involvement, including development of chronic renal failure. Patients with acute nephritic or nephrotic syndrome at presentation have a guarded renal prognosis, particularly if they are found to have concomitant necrosis or substantial crescentic changes on renal biopsy. Untreated, the risk of developing chronic kidney disease, including renal failure, is 2-5% in all patients with HSP, but almost 50% in those with the most severe early renal clinical and histologic features.

No studies have demonstrated any efficacy of short courses (weeks) of oral corticosteroids administered promptly after onset of HSP on either preventing the development of nephritis or decreasing the severity of subsequent HSP nephritis. Tonsillectomy has been proposed as an intervention for HSP nephritis, but it also does not appear to have any measurable effect on renal outcome. Mild HSP nephritis does not require treatment, because it usually resolves spontaneously.

Efficacy of treatment for moderate or severe HSP nephritis, which is far more likely to progress to chronic renal failure, is more difficult to assess. Limited prospective controlled trials for severe HSP nephritis have not shown benefit from any therapy studied. Several uncontrolled studies have reported significant benefit from aggressive immunosuppression (high-dose and extended courses of corticosteroids with cyclophosphamide or azathioprine) in patients with poor prognostic features on renal biopsy; such patients are at high risk of progressing to chronic renal failure based on historic controls. Anecdotal reports of treatment of high-risk patients with either plasmapheresis or rituximab have indicated a potential benefit. Balancing the absence of controlled data with the severe side effects of aggressive therapies in patients with poor renal prognostic factors is difficult. Aggressive therapy with careful monitoring may be reasonable in those with the most severe HSP nephritis (>50% crescents on biopsy).

Bibliography is available at Expert Consult.
Bibliography


Rapidly Progressive (Crescentic) Glomerulonephritis

Scott K. Van Why and Ellis D. Avner

“Rapidly progressive” describes the clinical course of several forms of glomerulonephritis whose unifying feature is the histopathologic finding of crescents in the majority of glomeruli (Fig. 516-1). The terms rapidly progressive glomerulonephritis (RPGN) and crescentic glomerulonephritis (CGN) are synonymous. The natural history of most forms of CGN is rapid and relentless progression to end-stage renal failure.

CLASSIFICATION

CGN can be a severe manifestation of essentially every defined primary and secondary glomerulonephritis (GN), but particular forms of GN are more likely to present as, or evolve into, RPGN (Table 516-1). If no underlying cause is identified by systemic features, serologic testing, or histologic examination, the disease is classified as idiopathic CGN. The incidence of specific etiologies of CGN in children varies widely; certain common themes are shared in all such reports. Patients with systemic vasculitis appear to be particularly prone to develop CGN. Patients with Henoch-Schönlein purpura (HSP), antineutrophil cytoplasmic antibody (ANCA)–mediated GN (microscopic polyangiitis and granulomatosis with polyangiitis), and systemic lupus erythematosus account for the majority of patients with CGN. Postinfectious GN or endocarditis rarely progresses to CGN, but because it is the most common form of GN in childhood it accounts for a significant percentage of patients with CGN in most reports. Membranoproliferative GN and idiopathic disease make up most of the remaining cases of CGN. Immunoglobulin (Ig) A nephropathy, a common GN, only rarely is rapidly progressive. Goodpasture disease often has rapidly progressive GN as a component of the syndrome, but its rarity in childhood results in its making up only a small percentage of children with CGN.

Table 516-1 Classification of Rapidly Progressive (“Crescentic”) Glomerulonephritis

<table>
<thead>
<tr>
<th>PRIMARY</th>
<th>Classification of Rapidly Progressive (“Crescentic”) Glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I: Anti–glomerular basement membrane antibody disease, Goodpasture syndrome (with pulmonary disease)</td>
<td></td>
</tr>
<tr>
<td>Type II: Immune complex mediated</td>
<td></td>
</tr>
<tr>
<td>Type III: Pauciimmune (usually antineutrophil cytoplasmic antibody-positive)</td>
<td></td>
</tr>
<tr>
<td>SECONDARY</td>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Immunoglobulin A nephropathy, Henoch-Schönlein purpura</td>
<td></td>
</tr>
<tr>
<td>Poststreptococcal glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa, hypersensitivity angiitis</td>
<td></td>
</tr>
</tbody>
</table>


PATHOLOGY AND PATHOGENESIS

The hallmark of CGN is the histopathologic finding of crescents in glomeruli (see Fig. 516-1). Crescent formation, through proliferation of parietal epithelial cells in Bowman’s space, may be the final pathway of any severe inflammatory glomerular injury. Podocytes and renal progenitor cells are involved in the pathogenesis of CGN. Fibrous crescents, in which proliferative cellular crescents are replaced by collagen, are a late finding. The immunofluorescence findings, as well as the pattern of any deposits by electron microscopy can delineate the underlying glomerulopathy in CGN secondary to lupus, HSP nephritis, membranoproliferative glomerulonephritis, postinfectious GN, IgA nephropathy, or Goodpasture disease. Rare or absent findings by immunofluorescence and electron microscopy typify pauciimmune GN (Wegener disease and microscopic polyangiitis) and idiopathic crescentic GN.

CLINICAL MANIFESTATIONS

Most children present with acute nephritis (hematuria, some degree of renal insufficiency, and hypertension) and usually have concomitant proteinuria, often with nephrotic syndrome. Occasional patients present late in the course of disease with oliguric renal failure. Extra-renal manifestations, such as pulmonary involvement, joint symptoms, or skin lesions, can help lead to the diagnosis of the underlying systemic disease causing the CGN.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of CGN is made by biopsy. Delineation of the underlying etiology is reached by a combination of additional biopsy findings (described earlier), extrarenal symptoms and signs, and serologic testing, including evaluation of antinuclear and anti-DNA antibodies, serum complement levels, and ANCA. If the patient has no extrarenal manifestations and a negative serologic evaluation, and if the biopsy has no immune or electron microscopy deposits, the diagnosis is idiopathic, rapidly progressive CGN.

PROGNOSIS AND TREATMENT

Although the outcome is not uniformly positive, children with crescentic postinfectious GN can spontaneously recover. The natural course of CGN is far more severe in the setting of other etiologies, including the idiopathic category, and progression to end-stage renal failure within weeks to months from onset is common. Having a majority of fibrous crescents on a renal biopsy portends a poor prognosis, because the disease usually has progressed to irreversible injury. Although there are few controlled data, the consensus of most nephrologists is that the combination of high-dose corticosteroids and cyclophosphamide may be effective in preventing progressive renal failure in patients with systemic lupus erythematosus, HSP nephritis, Wegener granulomatosis, and IgA nephropathy if given early in the course when acute cellular crescents predominate. Although such therapy can also be effective in the other diseases causing RPGN, renal outcomes in those settings are less favorable. Progression to end-stage renal disease often occurs despite aggressive immunosuppressive therapy. In combination with immunosuppression, plasmapheresis has been reported to
benefit patients with Goodpasture disease. Plasmapheresis may also benefit patients with ANCA-associated CGN, in particular those with the most severe renal dysfunction at presentation. The possible benefits of plasmapheresis in other forms of RPGN are unclear.

Bibliography is available at Expert Consult.
Bibliography
Goodpasture disease is characterized by pulmonary hemorrhage and glomerulonephritis. The disease results from attack on these organs by antibodies directed against certain epitopes of type IV collagen, located within the alveolar basement membrane in the lung and glomerular basement membrane (GBM) in the kidney. The production of pathologic autoantibody against specific domains in type IV collagen is triggered by an acquired conformational change in \( \alpha_{345N} \) hexamers, central structural elements in type IV collagen. The resulting structural alteration reveals neoepitopes that become the target of the pathogenic Goodpasture autoantibody.

**PATHOLOGY**

Kidney biopsy shows crescentic glomerulonephritis in most patients. Immunofluorescence microscopy demonstrates continuous linear deposition of immunoglobulin G along the GBM (Fig. 517-1).

**CLINICAL MANIFESTATIONS**

Goodpasture disease is rare in childhood. Patients usually present with hemoptysis from pulmonary hemorrhage that can be life-threatening. Concomitant renal manifestations include acute glomerulonephritis with hematuria, proteinuria, and hypertension, which usually follows a rapidly progressive course. Renal failure commonly develops within days to weeks of clinical presentation. Uncommonly, patients can have anti-GBM nephritis manifesting as isolated, rapidly progressive glomerulonephritis without pulmonary hemorrhage. In essentially all cases, serum anti-GBM antibody is present and complement C3 level is normal. Antineutrophilic cytoplasmic antibody levels can be found to be elevated along with the anti-GBM antibody; such patients doubly positive for these autoantibodies, who have severe disease at presentation, appear to have a more severe prognosis.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

The diagnosis is made by a combination of the clinical presentation of pulmonary hemorrhage with acute glomerulonephritis, the presence of serum antibodies directed against GBM (anti-type IV collagen in GBM), and characteristic renal biopsy findings. Other diseases that can cause a pulmonary-renal syndrome need to be considered and include systemic lupus erythematosus, Henoch-Schönlein purpura, granulomatosis with polyangiitis, nephrotic syndrome-associated pulmonary embolism, and microscopic polyangiitis. These diseases are ruled out by the absence of other characteristic clinical features, kidney biopsy findings, and negative serologic studies for antibodies against nuclear (antinuclear antibody), DNA (anti-dsDNA), and neutrophil cytoplasmic components (antineutrophilic cytoplasmic antibody).

**PROGNOSIS AND TREATMENT**

Untreated, the prognosis of Goodpasture disease is poor. The combination of high-dose intravenous methylprednisolone, cyclophosphamide, and plasmapheresis appears to improve survival. Nevertheless, patients who survive the pulmonary hemorrhage often progress to end-stage renal failure despite ongoing immunosuppressive therapy.

Bibliography is available at Expert Consult.
Bibliography


Hemolytic-uremic syndrome (HUS) is a common cause of community-acquired acute kidney injury in young children. It is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. HUS has clinical features in common with thrombotic thrombocytopenic purpura (TTP) (see Chapter 484.5). The etiology and pathophysiology of the more common forms of HUS clearly delineate childhood HUS as separate from idiopathic TTP.

**ETIOLOGY**

The various etiologies of HUS and other related thrombotic microangiopathies allow classification into infection-induced, genetic, medication-induced, and HUS associated with systemic diseases characterized by microvascular injury (Tables 518-1 and 518-2). The most common form of HUS is caused by toxin-producing *Escherichia coli* that causes prodromal acute enteritis and is commonly termed diarrhea-associated HUS. In the subcontinent of Asia and in southern Africa, the toxin of *Shigella dysenteriae* type 1 is causative, whereas in Western countries, verotoxin or Shiga-like toxin producing *E. coli* (STEC) is the usual cause.

Several serotypes of *E. coli* can produce the toxin; O157:H7 is most common in Europe and the Americas. A large epidemic of HUS in Europe was caused by Shiga toxin–producing *E. coli* O104:H4. The reservoir of STEC is the intestinal tract of domestic animals, usually cows. Disease commonly is transmitted by undercooked meat or unpasteurized (raw) milk and apple cider. Local outbreaks have followed ingestion of undercooked, contaminated hamburger or other foods cross-contaminated on unwashed cutting boards at fast food restaurants; contaminated municipal water supplies; petting farms; and swimming in contaminated ponds, lakes, or pools. With broad food distribution, wider epidemics have been traced to lettuce, raw spinach, and bean sprouts contaminated with STEC. Less often, STEC has been spread by person-to-person contact within families or child care centers. A rare but distinct entity of infection-triggered HUS is related
HUS can be superimposed on any disease associated with microvascular injury, including malignant hypertension, systemic lupus erythematosus, and antiphospholipid syndrome (see Chapter 484.4). It can also occur following bone marrow or solid organ transplantation, and may be triggered by the use of the calcineurin inhibitors cyclosporine and tacrolimus in that setting. Several other medications also can induce HUS (see Table 518-1).

### PATHOLOGY

Kidney biopsies are only rarely performed in HUS because the diagnosis is usually established by clinical criteria and the risks of biopsy are significant during the active phase of the disease. Early glomerular changes include thickening of the capillary walls caused by swelling of endothelial cells and accumulation of fibrillar material between endothelial cells and the underlying basement membrane, causing narrowing of the capillary lumens. Platelet–fibrin thrombi are often seen in glomerular capillaries. Thrombi are also seen in afferent arterioles and small arteries with fibrinoid necrosis of the arterial wall, leading to renal cortical necrosis from vascular occlusion. Late findings include glomerular sclerosis and obsolescence secondary to either severe direct glomerular involvement or glomerular ischemia from arteriolar involvement.

### PATHOGENESIS

Microvascular injury with endothelial cell damage is characteristic of all forms of HUS. In the diarrhea-associated form of HUS, enteropathic organisms produce either Shiga toxin or the highly homologous Shiga-like verotoxin both of which directly cause endothelial cell damage. Shiga toxin can directly activate platelets to promote their aggregation. In pneumococcal-associated HUS, neuraminidase cleaves sialic acid on membranes of endothelial cells, red cells, and platelets to reveal the underlying cryptic Thomsen-Friedenreich (T) antigen. Endogenous immunoglobulin M (IgM) recognizes the T antigen and triggers the microvascular angio genesis.

The familial recessive and dominant forms of HUS, including the inherited deficiencies of ADAMTS13 and regulators of the complement cascade, probably predispose patients to developing HUS but do not cause the disease per se, because these patients might not develop HUS until later childhood or even adulthood. In such cases, HUS is often triggered by an inciting event such as an infectious disease. The absence of ADAMTS13 impairs cleavage of von Willebrand factor multimers, which enhances platelet ag gre gation. Factor H plays a central role in complement regulation, primarily arresting amplification and propagation of complement activation. It is possible that mild endothelial injury that would normally resolve instead evolves to an aggressive microangiopathy because of the inherited deficiencies of these factors.

In each form of HUS, capillary and arteriolar endothelial injury in the kidney leads to localized thrombosis, particularly in glomeruli, causing a direct decrease in glomerular filtration. Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia. Microangiopathic hemolytic anemia results from mechanical damage to red blood cells as they pass through the damaged and thrombotic microvasculature.

### CLINICAL MANIFESTATIONS

HUS is most common in preschool and school-age children, but it can occur in adolescents and adults. In HUS caused by toxigenic Escherichia coli, onset of HUS occurs a few days after onset of gastroenteritis with fever, vomiting, abdominal pain, and diarrhea. The prodromal intestinal symptoms may be severe and require hospitalization, but they can also be relatively mild and considered trivial. The diarrhea is often bloody, but not necessarily so. Following the prodromal illness, the sudden onset of pallor, irritability, weakness, and lethargy heralds the onset of HUS. Oliguria can be present in early stages but may be masked by ongoing diarrhea, because the prodromal enteritis often overlaps the onset of HUS, particularly with ingestion of large doses of toxin. Thus, patients with HUS can present with either significant dehydration or volume overload, depending on whether the enteritis or renal
insufficiency from HUS predominates, and the amount of fluid that has been administered.

Patients with pneumococci-associated HUS usually are ill with pneumonia, empyema, and bacteremia when they develop HUS. Onset can be insidious in patients with the genetic forms of HUS, with HUS triggered by a variety of illnesses, including mild, nonspecific gastroenteritis or respiratory tract infections.

HUS can be relatively mild, or can progress to a severe and fatal multisystem disease. Leukocytosis, severe prodromal enteritis, hypotremia, and antibiotic use portend a severe course, but no presenting features reliably predict the severity of HUS in any given patient. Patients with HUS who appear mildly affected at presentation can rapidly develop severe, multisystem, life-threatening complications. Renal insufficiency can be mild but also can rapidly evolve into severe oliguric or anuric renal failure. The combination of rapidly developing renal failure and severe hemolysis can result in life-threatening hyperkalemia. Volume overload, hypertension, and severe anemia can all develop soon after onset of HUS, and together can precipitate heart failure. Direct cardiac involvement is rare, but pericarditis, myocardial dysfunction, or arrhythmias can occur without predisposing features of hypertension, volume overload, or electrolyte abnormalities.

The majority of patients with HUS have some central nervous system (CNS) involvement. Most have mild manifestations, with significant irritability, lethargy, or nonspecificencephalopathic features. Severe CNS involvement occurs in ≤20% of cases. Seizures and significant encephalopathy are the most common manifestations in those with severe CNS involvement, resulting from focal ischemia secondary to microvascular CNS thrombosis. Small infarctions in the basal ganglion and cerebral cortex have also been reported, but large strokes and intracranial hemorrhage are rare. Hypertension may produce an encephalopathy and seizures. Intestinal complications can be protein and include severe inflammatory colitis, ischemic enteritis, bowel perforation, intussusception, and pancreatitis. Patients can develop petechiae, but significant or severe bleeding is rare despite very low platelet counts.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**
The diagnosis is made by the combination of microangiopathic hemolytic anemia with schistocytes, thrombocytopenia, and some degree of kidney involvement. The anemia can be mild at presentation, but rapidly progresses. Thrombocytopenia is an invariable finding in the acute phase, with platelet counts usually 20,000-100,000/mm3. Partial thromboplastin and prothrombin times are usually normal. The Coombs test is negative, with the exception of pneumococci-induced HUS, where the Coombs test is usually positive. Leukocytosis is often present and significant. Urinalysis typically shows microscopic hematuria and low-grade proteinuria. The renal insufficiency can vary from mild elevations in serum blood urea nitrogen and creatinine to acute, anuric kidney failure.

The etiology of HUS is often clear with the presence of a diarrheal prodrome or pneumococcal infection. The presence or absence of toxigenic organisms on stool culture has little role in making the diagnosis of diarrhea-associated, enteropathogenic HUS. Only a minority of patients infected with those organisms develops HUS, and the organisms that cause HUS may be rapidly cleared. Therefore, the stool culture is often negative in patients who have diarrhea-associated HUS. If no history of diarrheal prodrome or pneumococcal infection is obtained, then evaluation for genetic forms of HUS should be considered, because these patients are at risk for recurrence, have a severe prognosis, and can benefit from different therapy. Other causes of acute kidney injury associated with a microangiopathic hemolytic anemia and thrombocytopenia should be considered and excluded, such as systemic lupus erythematosus, malignant hypertension, and bilateral renal vein thrombosis (see Table 518-1). A kidney biopsy is rarely indicated to diagnose HUS.

**PROGNOSIS AND TREATMENT**
With early recognition and intensive supportive care, the mortality for diarrhea-associated HUS is <5% in most major medical centers. Up to half of patients may require dialysis support during the acute phase of the disease. Most recover renal function completely, but of surviving patients, 5% remain dependent on dialysis, and up to 30% are left with some degree of chronic renal insufficiency. The prognosis for HUS not associated with diarrhea is more severe. Pneumococci-associated HUS causes increased patient morbidity, with mortality reported as 20%. The familial, genetic forms of HUS can be insidiously progressive or relapsing diseases and have a poor prognosis (see Table 518-2).

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**Table 518-2 Genetic Abnormalities and Clinical Outcome in Patients with Atypical Hemolytic-Uremic Syndrome**

<table>
<thead>
<tr>
<th>GENE</th>
<th>PROTEIN AFFECTED</th>
<th>MAIN EFFECT</th>
<th>FREQUENCY (%)</th>
<th>RESPONSE TO SHORT-TERM PLASMA THERAPY</th>
<th>LONG-TERM OUTCOME</th>
<th>OUTCOME OF KIDNEY TRANSPLANTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>Factor H</td>
<td>No binding to endothelium</td>
<td>20-30</td>
<td>Rate of remission: 60% (dose and timing dependent)</td>
<td>Rate of death or ESRD: 70-80%</td>
<td>Rate of recurrence: 80-90%†</td>
</tr>
<tr>
<td>CFHR1/3</td>
<td>Factor HR1, R3</td>
<td>Anti-factor H antibodies</td>
<td>6</td>
<td>Rate of remission: 70-80% (plasma exchange combined with immunosuppression)</td>
<td>Rate of ESRD: 30-40%</td>
<td>Rate of recurrence: 20%†</td>
</tr>
<tr>
<td>MCP</td>
<td>Membrane cofactor protein</td>
<td>No surface expression</td>
<td>10-15</td>
<td>No definitive indication for therapy</td>
<td>Rate of death or ESRD: &lt;20%</td>
<td>Rate of recurrence: 15-20%†</td>
</tr>
<tr>
<td>CFI</td>
<td>Factor I</td>
<td>Low level or low cofactor activity</td>
<td>4-10</td>
<td>Rate of remission: 30-40%</td>
<td>Rate of death or ESRD: 60-70%</td>
<td>Rate of recurrence: 70-80%†</td>
</tr>
<tr>
<td>CFB</td>
<td>Factor B</td>
<td>C3 convertase stabilization</td>
<td>1-2</td>
<td>Rate of remission: 30%</td>
<td>Rate of death or ESRD: 70%</td>
<td>Recurrence in one case</td>
</tr>
<tr>
<td>C3</td>
<td>Complement C3</td>
<td>Resistance to C3b inactivation</td>
<td>5-10</td>
<td>Rate of remission: 40-50%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Rate of recurrence: 40-50%</td>
</tr>
<tr>
<td>THBD</td>
<td>Thrombomodulin</td>
<td>Reduced C3b inactivation</td>
<td>5</td>
<td>Rate of remission: 60%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Recurrence in 1 patient</td>
</tr>
</tbody>
</table>

*Remission was defined as either complete remission or partial remission (i.e., hemolytic remission with renal sequelae).
†The long-term outcome was defined as the outcome 5-10 yr after onset.
‡Patients in this category were eligible for combined liver and kidney transplantation.
§Patients in this category were eligible for single kidney transplantation.
ESRD, end-stage renal disease.

Identification of specific factor deficiencies in some of these genetic forms provides opportunity for directed therapy to improve outcome.

The primary approach that has substantially improved acute outcome in HUS is early recognition of the disease, monitoring for potential complications, and meticulous supportive care. Supportive care includes careful management of fluid and electrolytes, including prompt correction of volume deficit, control of hypertension, and early institution of dialysis if the patient becomes significantly oliguric or anuric, particularly with hyperkalemia. Early intravenous volume expansion before the onset of oligo anuria may be nephroprotective in diarrhea-associated HUS. Red cell transfusions are usually required as hemolysis can be brisk and recurrent until the active phase of the disease has resolved. In pneumococci-associated HUS, it is critical that any administered red cells be washed before transfusion to remove residual plasma, because endogenous IgM directed against the revealed T antigen can play a role in accelerating the pathogenesis of the disease. Platelets should generally not be administered, regardless of platelet count, to patients with HUS because they are rapidly consumed by the active coagulation and theoretically can worsen the clinical course. Despite low platelet counts, serious bleeding is very rare in patients with HUS.

There is no evidence that any therapy directed at arresting the disease process of the most common, diarrhea-associated form of HUS provides benefit, and some can cause harm. Attempts have been made using anticoagulants, antiplatelet agents, fibrinolytic therapy, plasma therapy, immune globulin, and antibiotics. Anticoagulation, antiplatelet, and fibrinolytic therapies are specifically contraindicated because they increase the risk of serious hemorrhage. Antibiotic therapy to clear enteric toxigenic organisms (STEC) can result in increased toxin release, potentially exacerbating the disease, and therefore is not recommended. However, prompt treatment of causative pneumococcal infection is important. The European experience with E. coli O104:H4 in adults who were treated with azithromycin demonstrated more rapid elimination of the organism. Furthermore, in vitro evidence suggests that meropenem, rifaximin, and azithromycin downregulate the release and expression of Shiga toxin. Nonetheless in children with E. coli O157:H7–associated HUS, antibiotics are considered contraindicated.

Plasma infusion or plasmapheresis has been proposed for patients suffering severe manifestations of HUS with serious CNS involvement. There are no controlled data demonstrating the effectiveness of this approach, and it is specifically contraindicated in those with pneumococcal-associated HUS as it could exacerbate the disease. The use of plasma therapy in STEC–HUS was one of many treatment strategies during one of the largest reported outbreaks of STEC–HUS, which occurred in Europe in 2011. This outbreak was caused by an uncommon serotype (O104:H4) that had unique virulence factors. Thought initially to cause more severe disease, it differed epidemiologically from other STEC–HUS serotypes by affecting primarily healthy adults, rather than the usual pattern of affecting children and the elderly. Treatment in this epidemic included plasma exchange in most of the adult patients, as well as the use of eculizumab.

Eculizumab is an anti-C5 antibody that inhibits complement activation, a pathway that contributes to active disease in some forms of atypical familial HUS; this pathway may contribute to the process in STEC-HUS. Eculizumab is FDA approved for the treatment of atypical HUS. Because of the risk of meningococcal disease in patients with congenital defects in terminal complement components, it is recommended to give the meningococcal vaccine prior to giving eculizumab (if the patient has not been primarily immunized). While initial reports suggested that eculizumab provided benefit in patients with diarrhea-associated HUS, subsequent systematic analysis showed no benefit from either plasma exchange or eculizumab.

Plasma therapy can be of substantial benefit to patients with identified deficits of ADAMTS13 or factor H. It may also be considered in patients with other genetic forms of HUS, such as the undefined familial (recessive or dominant) form or sporadic but recurrent HUS. In contrast to its use in STEC-HUS, eculizumab shows great promise in treatment of atypical HUS, including HUS occurring following renal transplantation. Whether it should be combined with plasma therapy, or used as a primary treatment of atypical HUS, is still undetermined.

Most patients with diarrhea-associated HUS recover completely with little risk of long-term sequelae. Patients with hypertension, any level of renal insufficiency, or residual urinary abnormalities persisting a year after an episode of diarrhea-positive HUS (particularly significant proteinuria) require careful follow-up. Patients who have recovered completely with no residual urinary abnormalities after a yr are unlikely to manifest long-term sequelae. Because of some reports of late sequelae in such patients, annual examinations with a primary physician are still warranted.

Bibliography is available at Expert Consult.
Bibliography


Chapter 519
Upper Urinary Tract
Causes of Hematuria

519.1 Interstitial Nephritis
See Chapter 523.

519.2 Toxic Nephropathy
See Chapter 533.

519.3 Cortical Necrosis
See Chapter 534.

519.4 Pyelonephritis
See Chapter 538.

519.5 Nephrocalcinosis
See Chapter 547.

519.6 Vascular Abnormalities
Craig C. Porter and Ellis D. Avner

Hemangiomas, hemangiolympangiomas, angiomyomas, and arteriovenous malformations of the kidneys and lower urinary tract are rare causes of hematuria. They can present clinically with microscopic hematuria or gross hematuria with clots. When associated cutaneous vascular malformations are present, they can offer a clue to these underlying causes of hematuria. Renal colic can develop with any upper tract vascular abnormality that obstructs urinary drainage, induces an inflammatory response, or distends the renal capsule. The diagnosis may be confirmed by angiography or endoscopy.

Unilateral bleeding of varicose veins of the left ureter, resulting from compression of the left renal vein between the aorta and superior mesenteric artery (mesoaortic compression), is referred to as the nutcracker syndrome. Patients with this syndrome typically present with
Renal Vein Thrombosis
Craig C. Porter and Ellis D. Avner

**Epidemiology**
Renal vein thrombosis (RVT) occurs in 2 distinct clinical settings: (1) In newborns and infants, RVT is commonly associated with asphyxia, dehydration, shock, sepsis, congenital hypercoagulable states, and maternal diabetes; and (2) in older children, RVT is seen in patients with nephrotic syndrome, cyanotic heart disease, inherited hypercoagulable states, sepsis, following kidney transplantation, and following exposure to angiographic contrast agents.

**Pathogenesis**
RVT begins in the intrarenal venous circulation and can then extend to the main renal vein and even the inferior vena cava. Thrombus formation is mediated by endothelial cell injury resulting from hypoxia, endotoxin, or contrast media. Other contributing factors include hypercoagulability from either nephrotic syndrome or mutations in genes that encode clotting factors (i.e., factor V Leiden deficiency); hypovolemia and decreased venous blood flow associated with septic shock, dehydration, or nephrotic syndrome; and intravascular sludging caused by polycythemia.

**Clinical Manifestations**
The development of RVT is classically heralded by the sudden onset of gross hematuria and unilateral or bilateral flank masses. However, patients can also present with any combination of microscopic hematuria, flank pain, hypertension, or a microangiopathic hemolytic anemia with thrombocytopenia or oliguria. RVT is usually unilateral. Bilateral RVT results in acute kidney failure.

**Diagnosis**
The diagnosis of RVT is suggested by the development of hematuria and flank masses in patients seen in the high-risk clinical settings or with the predisposing clinical features noted above. Ultrasonography shows marked renal enlargement, and radiomucide studies reveal little or no renal function in the affected kidney(s). Doppler flow studies of the inferior vena cava and renal vein confirm the diagnosis. Contrast studies should be avoided to minimize the risk of further vascular damage.

**Differential diagnosis**
The differential diagnosis of RVT includes other causes of hematuria that are associated with rapid development of microangiopathic hemolytic anemia or enlargement of the kidney(s). These include hemolytic-uremic syndrome, hydronephrosis, polycystic kidney disease, Wilms tumor, and intrarenal abscess or hematoma. All patients should be evaluated for congenital and acquired hypercoagulable states.

**Treatment**
The primary treatment of RVT starts with aggressive supportive intensive care, including correction of fluid and electrolyte imbalance and treatment of renal insufficiency. The American College of Chest Physicians recommends that the additional initial treatment of bilateral RVT should include tissue plasminogen activator and unfractionated heparin followed by continued anticoagulation with unfractionated or low-molecular-weight heparin. Treatment recommendations for unilateral RVT with inferior vena cava extension include either unfractionated or low-molecular-weight heparin. There is no consensus as to whether unilateral RVT without extension should be managed with heparin or with supportive therapy alone. Aggressive treatment with thrombolytic agents in all of these clinical settings, as well as anti-thrombotic prevention of patients with documented thrombotic risk, remains controversial despite such recommendations given the significant risks of bleeding. Evidence-based data, particularly in children, do not exist despite such “best-practice” recommendations. Children with severe hypertension secondary to RVT who are refractory to antihypertensive medications may require nephrectomy.

**Prognosis**
Perinatal mortality from RVT has decreased significantly over the past 20 yr. Partial or complete renal atrophy is a common sequela of RVT in the neonate, leading to an increased risk of renal insufficiency, renal tubular dysfunction, and systemic hypertension. These complications are also seen in older children. However, recovery of renal function is not uncommon in older children with RVT resulting from nephrotic syndrome or cyanotic heart disease with correction of the underlying etiology.

**Idiopathic Hypercalciuria**
Craig C. Porter and Ellis D. Avner

Idiopathic hypercalciuria, which may be inherited as an autosomal dominant disorder, can clinically present as recurrent gross hematuria, persistent microscopic hematuria, dysuria, or abdominal pain in the absence of stone formation. Hypercalciuria can also accompany conditions resulting in hypercalcaemia, such as hyperparathyroidism, vitamin D intoxication, immobilization, and sarcoidosis. Hypercalciuria may be associated with Cushing syndrome, corticosteroid therapy, tubular dysfunction secondary to Fanconi syndrome (Wilson disease, oculocerebrorenal syndrome), Williams syndrome, distal renal tubular acidosis, or Bartter syndrome (see Chapter 531). Hypercalciuria may also be seen in patients with Dent disease, which is an X-linked form of nephrolithiasis associated with hypophosphatemic rickets. Although microcrystal formation with consequent tissue irritation is believed to mediate symptoms, the precise mechanism by which hypercalciuria causes hematuria or dysuria is unknown.

**Diagnosis**
Hypercalciuria is diagnosed by a 24 hr urinary calcium excretion >4 mg/kg. A screening test for hypercalciuria may be performed on a random urine specimen by measuring the calcium and creatinine concentrations. A spot urine calcium : creatinine ratio (mg/dL : mg/dL) >0.2 suggests hypercalciuria in an older child. Normal ratios may be as high as 0.8 in infants <7 mo of age.

**Treatment**
Left untreated, hypercalciuria leads to nephrolithiasis in approximately 15% of cases. Hypercalciuria has also been associated with an increased risk for development of low bone mineral density as well as an increased incidence of urinary tract infections. Idiopathic hypercalciuria has been identified as a risk factor in 40% of children with kidney stones, and a low urinary citrate level has been associated as a risk factor in approximately 38% of this group. Oral thiazide diuretics can normalize urinary calcium excretion by stimulating calcium reabsorption in the proximal and distal tubules. Such therapy can lead to resolution of gross hematuria or dysuria and can prevent nephrolithiasis. The precise indications for thiazide treatment (including its duration if initiated) remain controversial.

In patients with persistent gross hematuria or dysuria, therapy is initiated with hydrochlorothiazide at a dose of 1-2 mg/kg/24 hr as a single morning dose. The dose is titrated upward until the 24 hr urinary calcium excretion is <4 mg/kg and clinical manifestations

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Bibliography

resolve. After 1 yr of treatment, hydrochlorothiazide is usually discontinued, but may be resumed if gross hematuria, nephrolithiasis, or dysuria recurs. During hydrochlorothiazide therapy, the serum potassium level should be monitored periodically to avoid hypokalemia. Potassium citrate at a dose of 1 mEq/kg/24 hr may also be beneficial, particularly in patients with low urinary citrate excretion and symptomatic dysuria.

Sodium restriction is important because urinary calcium excretion parallels sodium excretion. Importantly, dietary calcium restriction is not recommended (except in children with massive calcium intake >250% of recommended dietary allowance by dietary history) because calcium is a critical requirement for growth, and no evidence supports a relationship between decreased calcium intake and decreased urinary calcium levels. This is particularly important given the association of hypercalciuria in some patients with reduced bone mineral density. A number of uncontrolled, small-scale studies support a role for bisphosphonate therapy, which leads to a reduction in urinary calcium excretion and improvement in bone mineral density. Controlled studies are necessary to establish a clear role for such therapy in children with hypercalciuria.

Bibliography is available at Expert Consult.
Bibliography

Chapter 520
Hematologic Diseases Causing Hematuria

520.1 Sickle Cell Nephropathy
Craig C. Porter and Ellis D. Avner

Gross or microscopic hematuria may be seen in children with sickle cell disease or sickle trait. Hematuria tends to resolve spontaneously in the majority of children (see Chapters 462.1 and 462.2). With the exception of an association with renal cell carcinoma, clinically apparent renal involvement occurs more commonly in patients with sickle cell disease than in those with sickle cell trait.

ETIOLOGY
The renal manifestations of sickle cell nephropathy (SSN) are generally related to microthrombosis secondary to sickling in the relatively hypoxic, acidic, hypertonic renal medulla where vascular stasis is present. Analgesic use, volume depletion with consequent prerenal failure, infection, and iron-related hepatic disease are independent contributing factors. Glomerular hyperfiltration, mediated by the intrarenal production of prostaglandins and synthesis of nitric oxide, is involved in the pathogenesis of proteinuria and kidney failure in SSN.

PATHOLOGY
Ischemia, papillary necrosis, and interstitial fibrosis are common pathologic findings in SSN. The specific sickle cell glomerular lesion consists of glomerular hypertrophy, with glomerulomegaly and distended capillaries. In addition, a variety of glomerular lesions are also found in SSN; most commonly these include focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and thrombotic microangiopathy. The pathophysiology of these specific glomerulonephritic lesions in SSN is poorly understood but is probably associated with the same factors that produce idiopathic or secondary disease as previously described (see Chapters 511-513).

CLINICAL MANIFESTATIONS
Clinical manifestations of SSN include polyuria caused by a urinary concentrating defect, renal tubular acidosis, and proteinuria associated with the glomerular lesions noted above.

Approximately 20-30% of patients with sickle cell disease develop proteinuria. Nephrotic-range proteinuria with or without clinically apparent nephrotic syndrome occurs in up to 30% of patients with SSN, and when present generally heralds progressive renal failure.

TREATMENT
Tubular manifestations have no specific treatment other than those recommended generally for patients with sickle cell disease. However, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor inhibitors can be used to effect a significant reduction in urine protein excretion in patients with daily urine protein excretion exceeding 500 mg, and may slow progression of renal failure. Gross hematuria secondary to papillary necrosis may respond to treatment with ε-aminocaproic acid or desmopressin acetate. Hydroxyurea and newer treatments for sickle cell disease (see Chapter 462.1) have decreased the manifestations of SSN in proportion to the other complications of the primary hemoglobinopathy.

PROGNOSIS
SSN can eventually lead to hypertension, renal insufficiency, and progressive kidney failure. Dialysis and eventual kidney transplantation are successful treatment modalities when kidney failure is irreversible.

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520.2 Coagulopathies and Thrombocytopenia
Craig C. Porter and Ellis D. Avner

Gross or microscopic hematuria may be associated with inherited or acquired disorders of coagulation (hemophilia, disseminated intravascular coagulation, thrombocytopenia). In these cases, however, hematuria is not usually the presenting complaint or a major factor affecting clinical management of outcome (see Chapters 475-484).
Bibliography


Gross or microscopic hematuria may be associated with many different types of malformations of the urinary tract. The sudden onset of gross hematuria after minor trauma to the flank is often associated with ureteropelvic junction obstruction, cystic kidneys, or enlarged kidneys from any cause (see Chapter 537).
521.2 Autosomal Recessive Polycystic Kidney Disease
Craig C. Porter and Ellis D. Avner

Also previously referred to as infantile polycystic disease, autosomal recessive polycystic kidney disease (ARPKD) is an autosomal recessive disorder occurring with an incidence of 1:10,000 to 1:40,000, and a gene carrier rate in the general population of 1/70. The gene for ARPKD (PKHD1 [polycystic kidney and hepatic disease]) encodes fibrocystin, a large protein (>4,000 amino acids) with multiple isoforms.

PATHOLOGY
Both kidneys are markedly enlarged and grossly show innumerable cysts throughout the cortex and medulla. Microscopic studies demonstrate dilated, ectatic collecting ducts radiating from the medulla to the cortex, although transient proximal tubule cysts have been reported in the fetus. Development of progressive interstitial fibrosis and tubular atrophy during advanced stages of disease eventually leads to renal failure. ARPKD causes dual-organ disease and should be considered as ARPKD/congenital hepatic fibrosis. Liver involvement is characterized by a basic ductal plate abnormality that leads to bile duct proliferation and ectasia, as well as progressive hepatic fibrosis.

PATHOGENESIS
Fibrocystin may form a multimeric complex with proteins of other primary genetic cystic diseases. It appears that altered intracellular signaling from these complexes, located at epithelial apical cell surfaces, intercellular junctions, and basolateral cell surfaces in association with the focal adhesion complex, is a critical feature of disease pathophysiology. A large number of mutations in PKHD1 (without identified specific “hot spots”) cause disease, and the same mutation can give variable degrees of disease severity in the same family. This clinical observation is consistent with preclinical data demonstrating many environmental and unknown genetic factors affecting disease expression. The false-negative rate for genetic diagnosis is approximately 10%. Limited available information suggests only gross genotype-phenotype correlation: mutations that modify fibrocystin appear to cause less-severe disease than those that truncate fibrocystin.

CLINICAL MANIFESTATIONS
The typical child presents with bilateral flank masses during the neonatal period or in early infancy. ARPKD may be associated with oligohydramnios, pulmonary hypoplasia, respiratory distress, and spontaneous pneumothorax in the neonatal period. Perinatal demise (approximately 25-30%) appears to be associated with truncating mutations. Components of the oligohydramnios complex (Potter syndrome), including low-set ears, micrognathia, flattened nose, limb-positioning defects, and intrauterine growth restriction, may be present at death from pulmonary hypoplasia. Hypertension is usually noted within the first few weeks of life, is often severe, and requires aggressive multidrug therapy for control. Oliguria and acute renal failure are uncommon, but transient hyponatremia, often in the presence of acute renal failure, often responds to diuresis. Renal function is usually impaired but may be initially normal in 20-30% of patients. Approximately 50% of patients with a neonatal-perinatal presentation develop end-stage renal disease (ESRD) by age 10 yr.

ARPKD is increasingly recognized in infants (and, rarely, in adolescents and young adults) with a mixed renal-hepatic clinical picture. Such children and young adults often present with predominantly hepatic manifestations in combination with variable degrees of renal disease. Hepatic disease manifests as portal hypertension, hepatosplenomegaly, gastrointestinal varices, episodes of ascending cholangitis, prominent cutaneous periumbilical veins, reversal of portal vein flow, and thrombocytopenia. Renal findings in patients with a hepatic presentation may range from asymptomatic abnormal renal ultrasonography to systemic hypertension and renal insufficiency. In the newborn, clinical evidence of liver disease by radiologic or clinical laboratory assessment is present in approximately 45% of children and believed to be universal by microscopic evaluation. Natural history studies of ARPKD patients presenting as infants and young children have classified this group in terms of the severity of their dual-organ phenotype: 40% severe renal/severe kidney and 20% of each of the following—severe kidney/mild liver, severe liver/mild kidney, and mild kidney/mild liver.

DIAGNOSIS
The diagnosis of ARPKD is strongly suggested by bilateral palpable flank masses in an infant with pulmonary hypoplasia, oligohydramnios, and hypertension and the absence of renal cysts by sonography of the parents (Fig. 521-1). Markedly enlarged and uniformly hyperecchogenic kidneys with poor corticomedullary differentiation are commonly seen on ultrasonography (Fig. 521-2). The diagnosis is supported by clinical and laboratory signs of hepatic fibrosis, pathologic findings of ductal plate abnormalities seen on liver biopsy, anatomic and pathologic proof of ARPKD in a sibling, or parental consanguinity. The diagnosis can be confirmed by genetic testing. The differential diagnosis includes other causes of bilateral renal enlargement and/or cysts, such as multicystic dysplasia, hydromeplasia, Wilms tumor, and bilateral renal vein thrombosis (Tables 521-1 and 521-2).

Nephronophthisis, an autosomal recessive disorder with renal fibrosis, tubular atrophy, and cyst formation is a common cause of ESRD in children and adolescents (Tables 521-1 and 521-2). Associated external findings include retinal degeneration (Senior-Loken syndrome), cerebellar ataxia (Joubert syndrome), and hepatic fibrosis (Boichis disease). Symptoms include polyuria (salt wasting, poor concentration ability), failure to thrive, and anemia. Hypertension and edema are seen later when ESRD develops. Prenatal diagnostic testing using genetic linkage analysis or direct mutation analysis is available in families with a previously affected child.

Preimplantation genetic diagnosis with in vitro fertilization may avoid the birth of another affected child with ARPKD.

TREATMENT
The current treatment of ARPKD is supportive. Aggressive ventilatory support is often necessary in the neonatal period secondary to pulmonary hypoplasia, hypventilation, and the respiratory illnesses of prematurity. Careful management of hypertension (angiotensin-converting enzyme inhibitors), fluid and electrolyte abnormalities, osteopenia, and clinical manifestations of renal insufficiency is essential. Children with severe respiratory failure or feeding intolerance from enlarged kidneys can require unilateral or, more commonly, bilateral nephrectomies, prompting the need for renal replacement therapy. For many children approaching ESRD therapy, significant portal hypertension is present. This in combination with the dramatic improvement in liver transplantation survival has led to consideration of dual renal and hepatic transplantation in a carefully selected group of patients. Dual transplantation thus avoids the later development of end-stage liver disease despite successful renal transplantation.

PROGNOSIS
Mortality has improved dramatically, although approximately 30% of patients die in the neonatal period from complications of pulmonary hypoplasia. Neonatal respiratory support and renal replacement therapies have increased the 10 yr survival of children surviving beyond the 1st yr of life to >80%. Fifteen-year survival is currently estimated at 70-80%. Consideration of dual renal and hepatic transplantation and the development of disease-specific therapies for pediatric clinical trials will further positively impact the natural history of ARPKD. An important resource for families of patients is the ARPKD/CHF Alliance (www.arpkdchf.org).

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### Table 521-1 Comparison of Clinical Features of Cystic Kidney Diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INHERITANCE</th>
<th>FREQUENCY</th>
<th>GENE PRODUCT</th>
<th>AGE OF ONSET</th>
<th>CYST ORIGIN</th>
<th>RENOMEGALY</th>
<th>CAUSE OF ESRD</th>
<th>OTHER MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPKD</td>
<td>AD</td>
<td>400-1,000</td>
<td>Polycystin 1, Polycystin 2</td>
<td>20s and 30s; &lt;2% before age 15</td>
<td>Anywhere (including the Bowman capsule)</td>
<td>Yes</td>
<td>Yes</td>
<td>Liver cysts, Cerebral aneurysms, Hypertension, Mitral valve prolapse, Kidney stones, UTIs</td>
</tr>
<tr>
<td>ARPKD</td>
<td>AR</td>
<td>6,000-10,000</td>
<td>Fibrocystin/polyductin</td>
<td>First yr of life; perinatal onset</td>
<td>Distal nephron, CD</td>
<td>Yes</td>
<td>Yes</td>
<td>Hepatic fibrosis, Pulmonary hypoplasia, Hypertension</td>
</tr>
<tr>
<td>ACKD</td>
<td>No</td>
<td>90% of ESRD patients at 8 yr</td>
<td>None</td>
<td>Years after onset of ESRD</td>
<td>Proximal and distal tubules</td>
<td>Rarely</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Simple cysts</td>
<td>No</td>
<td>50% in those older than 40 yr</td>
<td>None</td>
<td>Adulthood</td>
<td>Anywhere (usually cortical)</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>AR</td>
<td>80,000</td>
<td>Nephrocystins (NPHP1-9)</td>
<td>Childhood or adolescence</td>
<td>Medullary DCT</td>
<td>No</td>
<td>Yes</td>
<td>Retinal degeneration; neurologic, skeletal, hepatic, cardiac malformations</td>
</tr>
<tr>
<td>MCKD</td>
<td>AD</td>
<td>Rare</td>
<td>Uromodulin, others</td>
<td>Adulthood</td>
<td>Medullary DCT</td>
<td>No</td>
<td>Yes</td>
<td>Hyperuricemia, gout</td>
</tr>
<tr>
<td>MSK</td>
<td>No</td>
<td>5,000-20,000</td>
<td>None</td>
<td>30s</td>
<td>Medullary CD</td>
<td>No</td>
<td>No</td>
<td>Kidney stones, Hypercalciuria</td>
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<tr>
<td>Tuberous sclerosis</td>
<td>AD</td>
<td>10,000</td>
<td>Hamartin (TSC1), Tuberin (TSC2)</td>
<td>Childhood</td>
<td>Loop of Henle, DCT</td>
<td>Rarely</td>
<td>Rarely</td>
<td>Renal cell carcinoma, Tubers, seizures, Angiomyolipoma, Hypertension</td>
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<tr>
<td>VHL syndrome</td>
<td>AD</td>
<td>40,000</td>
<td>VHL protein</td>
<td>20s</td>
<td>Cortical nephrons</td>
<td>Rarely</td>
<td>Rarely</td>
<td>Retinal angioma, CNS hemangioblastoma, renal cell carcinoma, pheochromocytoma</td>
</tr>
<tr>
<td>Oral-facial-digital syndrome</td>
<td>XD</td>
<td>250,000</td>
<td>OFD1 protein</td>
<td>Childhood or adulthood</td>
<td>Renal glomeruli</td>
<td>Rarely</td>
<td>Yes</td>
<td>Malformation of the face, oral cavity, and digits; liver cysts; mental retardation</td>
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<tr>
<td>Bardet-Biedl syndrome</td>
<td>AR</td>
<td>65,000-160,000</td>
<td>BBS 14</td>
<td>Adulthood</td>
<td>Renal calyces</td>
<td>Rarely</td>
<td>Yes</td>
<td>Syndactyly and polydactyly, obesity, retinal dystrophy, male hypogenitalism, hypertension, mental retardation</td>
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</table>

ACKD, acquired cystic kidney disease; AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; ARPKD, autosomal recessive polycystic kidney disease; CD, collecting duct; CNS, central nervous system; DCT, distal convoluted tubule; ESRD, end-stage renal disease; MCKD, medullary cystic kidney disease; MSK, medullary sponge kidney; UTI, urinary tract infection; VHL, von Hippel-Lindau; XD, X-linked dominant.

Anatomic Abnormalities Associated with Hematuria

Table 521-2 | Autosomal Recessive Polycystic Kidney Disease and Hepatorenal Fibrocystic Disease Phenocopies

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>GENE(S)</th>
<th>RENAL DISEASE</th>
<th>HEPATIC DISEASE</th>
<th>SYSTEMIC FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARPKD</td>
<td>PKHD1</td>
<td>Collecting duct dilation</td>
<td>CHF; Caroli disease</td>
<td>No</td>
</tr>
<tr>
<td>ADPKD</td>
<td>PKD1; PKD2</td>
<td>Cysts along entire nephron</td>
<td>Biliary cysts; CHF (rare)</td>
<td>Yes: adults</td>
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<tr>
<td>NPHP</td>
<td>NPHP1-NPHP16</td>
<td>Cysts at the corticomedullary junction</td>
<td>CHF</td>
<td>+/-</td>
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<tr>
<td>Joubert syndrome and related disorders</td>
<td>JBTS1-JBTS20</td>
<td>Cystic dysplasia; NPHP</td>
<td>CHF, Caroli disease</td>
<td>Yes</td>
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<td>Bardet-Biedel syndrome</td>
<td>BBS1-BBS18</td>
<td>Cystic dysplasia; NPHP</td>
<td>CHF</td>
<td>Yes</td>
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<td>Meckel-Gruber syndrome</td>
<td>MKS1-MKS10</td>
<td>Cystic dysplasia</td>
<td>CHF</td>
<td>Yes</td>
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<td>Oral-facial-digital syndrome, type 1</td>
<td>OFD1</td>
<td>Glomerular cysts</td>
<td>CHF (rare)</td>
<td>Yes</td>
</tr>
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<td>Glomerulocystic disease</td>
<td>PKD1; HNF1B; UMOD</td>
<td>Enlarged; normal or hypoplastic kidneys</td>
<td>CHF (with PKD1 mutations)</td>
<td>+/-</td>
</tr>
<tr>
<td>Jeune syndrome (asphyxiating thoracic dystrophy)</td>
<td>IFT80 (ADT2) DYN2CH1 (ADT3) ADT1, ADT4, ADT5</td>
<td>Cystic dysplasia</td>
<td>CHF, Caroli disease</td>
<td>Yes</td>
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<td>Renal-hepatic-pancreatic dysplasia (Ivemark II)</td>
<td>NPHP3, NEK8</td>
<td>Cystic dysplasia</td>
<td>Intrahepatic biliary dysgenesis</td>
<td>Yes</td>
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<td>Zellweger syndrome</td>
<td>PEX1-3;5-6;10-11,13,14,16,19,26</td>
<td>Renal cortical microcysts</td>
<td>Intrahepatic biliary dysgenesis</td>
<td>Yes</td>
</tr>
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</table>

NPHP, Nephronophthisis. CHF, congenital hepatic fibrosis.


Figure 521-1 Infant with infantile polycystic kidney disease. A, This infant shows marked abdominal distention and bilaterally enlarged kidneys, as indicated by the outlined area. B, Intravenous pyelogram of the same patient shows the characteristic mottled nephrogram with brush-like medullary opacification secondary to retention of contrast material in dilated cortical and medullary collecting ducts. (From Zitelli BJ, Davis HW, editors: Atlas of pediatric physical diagnosis, ed 4, St. Louis, 2002, Mosby, p. 470.)

521.3 Autosomal Dominant Polycystic Kidney Disease

Craig C. Porter and Ellis D. Avner

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary human kidney disease, with an incidence of 1/400 to 1/1,000. It is a systemic disorder with possible cyst formation in multiple organs (liver, pancreas, spleen, brain) and the development of saccular cerebral aneurysms.

PATHOLOGY

Both kidneys are enlarged and show cortical and medullary cysts originating from all regions of the nephron.

PATHOGENESIS

Approximately 85% of patients with ADPKD have mutations that map to the PKD1 gene on the short arm of chromosome 16, which encodes polycystin, a transmembrane glycoprotein. Another 10–15% of ADPKD mutations map to the PKD2 gene on the long arm of chromosome 4, which encodes polycystin 2, a proposed nonselective cation channel.
The majority of mutations appear to be unique to a given family. At present, a mutation can be found in 85% of patients with well-characterized disease. Approximately 8–10% of patients will have de novo, disease-causing mutations. Mutations of PKD1 are associated with more severe renal disease than mutations of PKD2. The pathophysiology of the disease appears to be related to disruption of normal multimeric cystoprotein complexes, with consequent abnormal intracellular signaling resulting in abnormal proliferation, tubular secretion, and cyst formation. Abnormal growth factor expression, coupled with low intracellular calcium and elevated cyclic adenosine monophosphate, appear to be important features leading to formation of cysts and progressive enlargement.

**CLINICAL PRESENTATION**

The severity of renal disease and the clinical manifestations of ADPKD are highly variable. Although symptomatic ADPKD commonly occurs in the 4th or 5th decade of life, symptoms, including gross or microscopic hematuria, bilateral flank pain, abdominal masses, hypertension, and urinary tract infection, may be seen in neonates, children, and adolescents. With the increased utilization of abdominal sonography in the pediatric population, as well as ADPKD families now requesting possible screening in their asymptomatic, at-risk offspring (with the passage of the Genetic Information Nondiscrimination Act in the United States), most children with ADPKD are diagnosed by abnormal renal sonography in the absence of symptoms. Renal ultrasonography usually demonstrates multiple bilateral macrocysts in enlarged kidneys (Fig. 521-3), although normal kidney size and unilateral disease may be seen in the early phase of the disease in children.

ADPKD is a multiorgan disorder affecting many tissue types. Cysts may be asymptomatic but present within the liver, pancreas, spleen, and ovaries and when present help confirm the diagnosis in childhood. **Intracranial aneurysms**, which appear to segregate within certain families, have an overall prevalence of 15% and are an important cause of mortality in adults, but occasionally occur in children. Mitral valve prolapse is seen in approximately 12% of children; aortic and coronary artery aneurysms and aortic valve insufficiency are noted in affected adults. Hernias, bronchiectasis, and intestinal diverticula can also occur in these children.

**DIAGNOSIS**

ADPKD is confirmed by the presence of enlarged kidneys with bilateral macrocysts in a patient with an affected 1st-degree relative. De novo mutations occur in 8–10% of patients with newly diagnosed disease. The diagnosis might be made in children before their affected parent, making parental renal sonography an important diagnostic test to be performed in families with no apparent family history. Among patients with genetically defined ADPKD, screening renal ultrasonography results may be normal in ≤20% by 20 yr of age and <3% by 30 yr of age.

Prenatal diagnosis is suggested from the presence of enlarged kidneys with or without cysts on ultrasonography in families with known ADPKD. Prenatal DNA testing is available in families with affected members whose disease is caused by identified mutations in the PKD1 or PKD2 genes.

The differential diagnosis includes renal cysts associated with glomerulocystic kidney disease, tuberous sclerosis, and von Hippel-Lindau disease, which may be inherited in an autosomal dominant pattern (see Table 521-1). The neonatal manifestations of ADPKD and ARPKD may rarely be indistinguishable.

**TREATMENT AND PROGNOSIS**

Treatment of ADPKD is primarily supportive. Control of blood pressure is critical because the rate of disease progression in ADPKD correlates with the presence of hypertension. Angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists are agents of choice. Obesity, caffeine ingestion, smoking, multiple pregnancies, male gender, and possibly the use of calcium channel blockers appear to accelerate disease progression. Older patients with a family history of intracranial aneurysm rupture should be screened for cerebral aneurysms.

Although neonatal ADPKD may be fatal, long-term survival of the patient and the kidneys is possible for children surviving the neonatal period. ADPKD that occurs initially in older children has a favorable prognosis, with normal renal function during childhood seen in >80% of children.

Although disease-specific therapy is not yet available, a number of clinical trials are in progress based on promising preclinical laboratory investigation (www.clinicaltrials.gov). A valuable resource for patients and their families is the Polycystic Kidney Disease Foundation (www.pkdcure.org).

**521.4 Trauma**

*Craig C. Porter and Ellis D. Avner*

Infants and children are more susceptible to renal injury following blunt or penetrating injury to the back or abdomen because of their
Bibliography
decreased muscle mass “protecting” the kidney. Gross or microscopic hematuria, flank pain, and abdominal rigidity can occur; associated injuries may be present (see Chapter 72). In the absence of hemodynamic instability, most renal trauma can be managed nonoperatively. Urethral trauma can result from crush injury, often associated with a fractured pelvis or from direct injury. Such injury is suspected in the appropriate clinical setting when gross blood appears at the external urethral meatus. Rhabdomyolysis and consequent renal failure is another complication of crush injury that can be ameliorated by vigorous fluid resuscitation. There may be a relationship between microscopic hematuria and recreational accidents in individuals >16 yr of age, none of whom exhibited hypotension or required surgical intervention.

Bibliography is available at Expert Consult.

521.5 Renal Tumors
See Chapters 498 and 499.
Bibliography
522.1 Infectious Causes of Cystitis and Urethritis

Priya Pais and Ellis D. Avner

Gross or microscopic hematuria may be associated with bacterial, mycobacterial, or viral infections of the bladder (see Chapter 538).

522.2 Hemorrhagic Cystitis

Priya Pais and Ellis D. Avner

Hemorrhagic cystitis is defined as the presence of sustained hematuria and lower urinary tract symptoms (e.g., dysuria, frequency, urgency) in the absence of other bleeding conditions such as vaginal bleeding, a generalized bleeding condition, or a bacterial urinary tract infection. Depending on the severity, patients can present with microscopic or gross hematuria, often with clots. In severe forms, bleeding can lead to a significant decrease in blood hemoglobin levels.

Hemorrhagic cystitis can occur in response to chemical toxins (cyclophosphamide, penicillins, busulfan, thiotepa, dyes, insecticides), viruses (adenovirus types 11 and 21 [see Chapter 262] and influenza A), radiation, and amyloidosis. The polyoma BK virus, present latently in immunocompetent hosts, is associated with the development of drug-induced cystitis in immunosuppressed patients. The pediatric bone marrow transplantation population is particularly susceptible to hemorrhagic cystitis.

For chemical irritation related to use of cyclophosphamide, hydration and the use of mesna disulfide, which inactivates urinary cyclophosphamide metabolites, help to protect the bladder. Administration of oral cyclophosphamide in the morning followed by aggressive oral hydration throughout the remainder of the day is very effective in minimizing the risk of hemorrhagic cystitis. Treatment of hemorrhagic cystitis consists of a combination of intensive intravenous hydration, forced diuresis, analgesia, and spasmolytic drugs. Consultation with a urologist is recommended for more invasive measures if the cystitis does not respond to conservative measures. Gross hematuria associated with viral hemorrhagic cystitis usually resolves within 1 wk.

Bibliography is available at Expert Consult.

522.3 Vigorous Exercise

Priya Pais and Ellis D. Avner

Gross or microscopic hematuria can follow vigorous exercise. Exercise hematuria is less common in females and can be associated with dysuria. Approximately 30-60% of runners completing marathons have dipstick-positive urine for blood. In limited follow-up, none appeared to have any significant urinary tract abnormalities. The color of the urine following vigorous exercise can vary from red to black. Blood clots may be rarely present in the urine. Findings on urine culture, intravenous pyelography, voiding cystourethrography, and cystoscopy are normal in most patients. This seems to be a benign condition, and the hematuria generally resolves within 48 hr after cessation of exercise. The absence of red blood cell casts or evidence of renal disease and the presence of dysuria and blood clots in some patients suggest that the source of bleeding lies in the lower urinary tract. Rhabdomyolysis with myoglobinuria or hemoglobinuria must be considered in the differential diagnosis when associated with symptoms in the appropriate clinical context. Hydroh nephrosis or anatomic abnormalities must be considered in any child who presents with hematuria (particularly gross) after mild exercise or following mild trauma. Appropriate imaging studies are indicated in this setting.

Bibliography is available at Expert Consult.
Bibliography


Bibliography
NORMAL PHYSIOLOGY
The charge and size selective properties of the glomerular capillary wall prevent significant amounts of albumin, globulin, and other large plasma proteins from entering the urinary space (see Chapter 508). Smaller proteins (low-molecular-weight proteins) do cross the capillary wall but are reabsorbed by the proximal tubule. A very small amount of protein that normally appears in the urine is the result of normal tubular secretion. The normally excreted protein mostly consists of Tamm-Horsfall protein (uromodulin), a protective glycoprotein secreted by the tubules that inactivates cytokines.

PATHOPHYSIOLOGY OF PROTEINURIA
Abnormal amounts of protein may appear in the urine from 3 possible mechanisms: glomerular proteinuria, which occurs as a result of
disruption of the glomerular capillary wall; tubular proteinuria, a tubular injury or dysfunction that leads to ineffective reabsorption of mostly low-molecular-weight proteins; and increased production of plasma proteins— in multiple myeloma, rhabdomyolysis, or hemolysis—which may cause the production or release of very large amounts of protein that are filtered at the glomerulus and overwhelm the absorptive capacity of the proximal tubule.

**MEASUREMENT OF URINE PROTEIN**

Urine protein can be measured in random collected samples or in timed (e.g., 24 hr or overnight) samples. Tests to accurately quantify urine protein concentration rely on precipitation with sulfosalicylic acid and measurement of turbidity (Table 523-1).

### Urine Dipstick Measurement of Protein

Total protein concentration in urine can be estimated with chemically impregnated plastic strips that contain a pH-sensitive colorimetric indicator that changes color when negatively charged proteins, such as albumin, bind to it. Dipsticks primarily detect albuminuria and are less sensitive for other forms of proteins (low-molecular-weight proteins, Bence Jones protein, gamma globulins). Visual changes in the color of the dipstick are a semiquantitative measure of urinary protein concentration. The dipstick is reported as negative, trace (10-29 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), 3+ (300-1000 mg/dL), and 4+ (>1000 mg/dL). False-positive results can occur with a very high urine pH (>7.0), a highly concentrated urine specimen, or contamination of the urine with blood. False-negative test results can occur in patients with dilute urine or a large volume of urine output or in disease states in which the predominant urinary protein is not albumin.

**Positive urine dipstick test for protein** is considered to be present if there is more than a trace (10-29 mg/dL) in a urine sample in which the specific gravity is <1.010. If the specific gravity is >1.015, the dipstick must read ≥1+ (>30 mg/dL) to be considered clinically significant.

Because the dipstick reaction offers only a qualitative measurement of urinary protein excretion, children with persistent proteinuria should have proteinuria quantitated more precisely. **Timed (24 hr) urine collections** offer more precise information regarding urinary protein excretion than a randomly performed dipstick test. Urinary protein excretion in the normal child is less than 100 mg/m²/day or a total of 150 mg/day. In neonates, normal urinary protein excretion is higher, up to 300 mg/m², because of reduced reabsorption of filtered proteins. A reasonable upper limit of normal protein excretion in healthy children is 150 mg/24 hr. More specifically, normal protein excretion in children is defined as ≤4 mg/m²/hr; abnormal proteinuria is defined as excretion of 4-40 mg/m²/hr; and nephrotic-range proteinuria is defined as >40 mg/m²/hr.

**Timed urine** collections are cumbersome to obtain, and the sensitivity and specificity of the test can be influenced by fluid intake, the volume of urine output, and the importance of including a complete collection without missed voids.

### Urine Protein-to-Creatinine Ratio Measurement

Urine protein-to-creatinine ratio measurement of an untimed (spot) urine specimen has largely replaced timed urine collection. In children, urine protein-to-creatinine ratios have been shown to significantly correlate with measurements of 24 hr urine protein and are useful to screen for proteinuria and to longitudinally monitor urine protein levels.

This ratio is calculated by dividing the urine protein concentration (mg/dL) by the urine creatinine concentration (mg/dL) to provide a simple measure. It should be ideally performed on a first morning voided urine specimen to eliminate the possibility of orthostatic (pos- tural) proteinuria (see Chapter 525). A ratio of <0.5 in children <2 yr of age and <0.2 in children >2 yr of age suggests normal urinary protein excretion. A ratio greater than 2 suggests nephrotic-range proteinuria.

### CLINICAL CONSIDERATIONS

The finding of proteinuria in children and adolescents in a single, non–first morning urine specimen is common, varying between 5% and 15%. The prevalence of persistent proteinuria on repeated testing is much less common. The challenge is to differentiate the child with proteinuria related to renal disease from the otherwise healthy child with transient or other benign forms of proteinuria. When proteinuria is detected, it is important to determine if it is transient, orthostatic, or fixed in nature.

**Microalbuminuria** is defined as the presence of albumin in the urine above the normal level but below the detectable range of conventional urine dipstick methods. In adults, persistent microalbuminuria (defined as a urinary albumin excretion of 30-300 mg/g creatinine on at least 2-3 samples) is accepted as evidence of diabetic nephropathy and also a predictor of cardiovascular and renal disease. The mean level of urinary albumin excretion falls between 8 and 10 mg/g of creatinine in children >6 yr of age. Similar to adults, microalbuminuria in children has been found to be associated with obesity and to predict, with reasonable specificity, the development of diabetic nephropathy in type 1 diabetes mellitus.

Bibliography is available at Expert Consult.
Bibliography
The majority of children found to have positive tests for protein on urinary dipsticks will have negative evaluations on repeated dipsticks and normal urinary protein if formally quantitated. Approximately 10% of children who undergo random urinalysis have proteinuria by a single dipstick measurement. Across the school-age spectrum, this finding occurs more commonly in adolescents than in younger children. In most cases, serial testing of the patient's urine demonstrates resolution of the abnormality. This phenomenon defines transient proteinuria, and its cause remains elusive. Defined contributing factors include a temperature >38.3°C (101°F), exercise, dehydration, cold exposure, heart failure, seizures, or stress. Transient proteinuria usually does not exceed 1-2+ on the dipstick. No evaluation or therapy is needed for children with this benign condition. Persistence of proteinuria, even if low grade, is not consistent with the diagnosis and suggests the need for additional evaluation.

Bibliography is available at Expert Consult.
Bibliography
Hogg RJ: Adolescents with proteinuria and/or the nephritic syndrome, Adolesc
Orthostatic proteinuria is the most common cause of persistent proteinuria in school-age children and adolescents, occurring in up to 60% of children with persistent proteinuria. Children with this condition are usually asymptomatic, and the condition is discovered by routine urinalysis. Patients with orthostatic proteinuria excrete normal or minimally increased amounts of protein in the supine position. In the upright position, urinary protein excretion may be increased 10-fold, up to 1,000 mg/24 hr (1 g/24 hr). Hematuria, hypertension, hypalbuminemia, edema, and renal dysfunction are absent.

In a child with persistent asymptomatic proteinuria, the initial evaluation should include an assessment for orthostatic proteinuria. It begins with the collection of a first morning urine sample, with subsequent testing of any urinary abnormalities by a complete urinalysis and determination of a spot protein : creatinine (Pr : Cr) ratio. The correct collection of the first morning urine sample is critical. The child must fully empty the bladder before going to bed and then collect the first voided urine sample immediately upon arising in the morning. The absence of proteinuria (dipstick negative or trace for protein; and a normal ratio of urinary protein [mg/dL] to urinary creatinine [mg/dL] = [uPr/uCr] <0.2) on the first morning urine sample for 3 consecutive days confirms the diagnosis of orthostatic proteinuria. No further evaluation is necessary, and the patient and family should be reassured of the benign nature of this condition. However, if there are other abnormalities of the urinalysis (e.g., hematuria), or if the urine uPr : uCr ratio is >0.2, the patient should be referred to a pediatric nephrologist for a complete evaluation.

The cause of orthostatic proteinuria is unknown, although altered renal hemodynamics and partial left renal vein obstruction in the upright, lordotic position have been proposed as possible causes.

Increased body mass index is recognized as a strong correlate of orthostatic proteinuria. Long-term follow-up studies in young adults suggest that orthostatic proteinuria is a benign process, but similar data are not available for children. Therefore, long-term follow-up of children is prudent. Patients should be monitored for the development of nonorthostatic proteinuria, particularly in the presence of hematuria, hypertension, or edema. Such findings may herald underlying kidney disease.

Bibliography is available at Expert Consult.
Bibliography


Children found to have fixed proteinuria on a first morning urine sample on 3 separate occasions should be further investigated. Fixed proteinuria is defined as a first morning urine sample that is ≥ 1+ on dipstick testing with a urine specific gravity > 1.015 or with a protein-to-creatinine ratio of ≥ 0.2. Fixed proteinuria indicates a potential kidney disease caused by either glomerular or tubular disorders.

526.1 Glomerular Proteinuria

The glomerular capillary wall consists of 3 layers: the fenestrated capillary endothelium, the glomerular basement membrane, and the podocytes (with foot processes and intercalated slit diaphragms) (Fig. 526-1). Glomerular proteinuria results from alterations in the permeability of any of the layers of the glomerular capillary wall to normally filtered proteins and occurs in a variety of renal diseases (Table 526-1). Glomerular proteinuria can range widely from < 1 g to > 30 g of protein in a 24 hr period. The podocyte is the predominant cell of injury in most glomerular diseases characterized by heavy proteinuria.

Glomerular proteinuria should be suspected in any patient with a first morning urine protein:creatinine ratio > 1.0, or significant proteinuria of any degree, accompanied by hypertension, hematuria, edema, or renal dysfunction (elevated blood urea nitrogen, creatinine). Disorders characterized primarily by proteinuria include idiopathic (minimal change) nephrotic syndrome, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, diabetic nephropathy, and obesity-related glomerulopathy. Other renal disorders that can include proteinuria as a prominent feature include acute postinfectious glomerulonephritis, immunoglobulin A nephropathy, lupus nephritis, Henoch-Schönlein purpura nephritis, and Alport syndrome.

Initial evaluation of a child with fixed proteinuria should include measurement of serum creatinine and electrolyte panel, first morning urine protein:creatinine ratio, serum albumin level, and complement levels. The child should be referred to a pediatric nephrologist for further evaluation and management. Renal biopsy is often necessary to establish a diagnosis and guide therapy.

In asymptomatic patients with low-grade proteinuria (protein:creatinine ratio between 0.2 and 1.0) in whom all other findings are normal, renal biopsy might not be indicated because the underlying process may be transient or resolving or because specific pathologic features of a chronic kidney disease might not yet be apparent. Such patients should have periodic reevaluation (ideally every 4-6 mo unless the patient is symptomatic). The evaluation should consist of a physical examination with accurate blood pressure measurement, urinalysis, measurement of serum creatinine and a repeat first morning urine
Figure 526-1 Glomerular capillary wall. The 3 layers of the capillary wall (glomerular endothelial cell, glomerular basement membrane [GBM], and podocyte) act as the glomerular filtration barrier (GFB), preventing proteins and large molecules from passing from the capillary lumen into the urinary space. The podocyte cell body lies within the urinary space, and the cell is attached to the GBM through foot processes. Adjacent foot processes are separated by the filtration slit, bridged by the slit diaphragm. Disruption of the GFB leads to the passage of protein across the capillary wall, leading to proteinuria. (From Jefferson JA, Nelson PJ, Najafian B, Shankland SJ. Podocyte disorders: core curriculum 2011. Am J Kidney Dis 58:666–677, 2011, Fig 1.)

Table 526-1 Causes of Proteinuria

<table>
<thead>
<tr>
<th>TRANSIENT PROTEINURIA</th>
<th>GLOMERULAR DISEASES WITH PROTEINURIA AS A PROMINENT FEATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Acute postinfectious glomerulonephritis (streptococcal, endocarditis, hepatitis B or C virus, HIV)</td>
</tr>
<tr>
<td>Exercise</td>
<td>Immunoglobulin A nephropathy</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Henoch-Schönlein purpura nephritis</td>
</tr>
<tr>
<td>Cold exposure</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Serum sickness</td>
</tr>
<tr>
<td>Seizure</td>
<td>Alport syndrome</td>
</tr>
<tr>
<td>Stress</td>
<td>Vasculitic disorders</td>
</tr>
<tr>
<td></td>
<td>Reflex nephropathy</td>
</tr>
</tbody>
</table>

| ORTHOSTATIC (POSTURAL) PROTEINURIA                        |                                                                            |
|-----------------------------------------------------------|                                                                            |

| GLOMERULAR DISEASES CHARACTERIZED BY ISOLATED PROTEINURIA |                                                                            |
|-----------------------------------------------------------|                                                                            |
| Idiopathic (minimal change) nephrotic syndrome            |                                                                            |
| Focal segmental glomerulosclerosis                        |                                                                            |
| Mesangial proliferative glomerulonephritis                |                                                                            |
| Membranous nephropathy                                    |                                                                            |
| Membranoproliferative glomerulonephritis                  |                                                                            |
| Amyloidosis                                               |                                                                            |
| Diabetic nephropathy                                      |                                                                            |
| Sickle cell nephropathy                                   |                                                                            |

| TUBULAR DISEASES                                          |                                                                            |
|-----------------------------------------------------------|                                                                            |
| Cystinosis                                                |                                                                            |
| Wilson disease                                            |                                                                            |
| Lowe syndrome                                             |                                                                            |
| Dent disease (X-linked recessive nephrolithiasis)         |                                                                            |
| Galactosemia                                              |                                                                            |
| Tubulointerstitial nephritis                             |                                                                            |
| Acute tubular necrosis                                    |                                                                            |
| Renal dysplasia                                           |                                                                            |
| Polycystic kidney disease                                 |                                                                            |
| Reflex nephropathy                                        |                                                                            |
| Drugs (penicillamine, lithium, NSAID)                     |                                                                            |
| Heavy metals (lead, gold, mercury)                        |                                                                            |

NSAID, nonsteroidal antiinflammatory drug.
protein:creatinine ratio. Indications for renal biopsy include increasing proteinuria (protein:creatinine >1.0) or the development of hematuria, hypertension, or diminished renal function.

Bibliography is available at Expert Consult.

526.2 Tubular Proteinuria

Priya Pais and Ellis D. Avner

A variety of renal disorders that primarily involve the tubulointerstitial compartment of the kidney can cause low-grade fixed proteinuria (protein:creatinine ratio 0.2:1.0). In the healthy state, large amounts of proteins of lower molecular weight than albumin are filtered by the glomerulus and reabsorbed in the proximal tubule. Injury to the proximal tubules can result in diminished reabsorptive capacity and the loss of these low-molecular-weight proteins in the urine.

Tubular proteinuria (see Table 526-1) may be seen in acquired and inherited disorders and may be associated with other defects of proximal tubular function, such as the Fanconi syndrome (glycosuria, phosphaturia, bicarbonate wasting, and aminoaciduria). Tubular proteinuria is a consistent finding among patients with the X-linked tubular syndrome, Dent disease, caused by mutations of the renal chloride channel.

Asymptomatic patients having persistent proteinuria generally have glomerular rather than tubular proteinuria. In occult cases, glomerular and tubular proteinuria can be distinguished by electrophoresis of the urine. In tubular proteinuria, little or no albumin is detected, whereas in glomerular proteinuria, the major protein is albumin.

Bibliography is available at Expert Consult.
Bibliography

Bibliography

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic-range) proteinuria. Nephrotic-range proteinuria is defined as proteinuria >3.5 g/24 hr or a urine protein:creatinine ratio >2. The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein are hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL).

Nephrotic syndrome affects 1-3 per 100,000 children <16 yr of age. Without treatment, nephrotic syndrome in children is associated with a high risk of death, most commonly from infections. Fortunately, 80% of children with nephrotic syndrome respond to corticosteroid therapy. Although glucocorticoid therapy is standard therapy for nephrotic syndrome, neither the target cell nor the mechanism of action of steroids has been determined. Early referral to a pediatric nephrologist is recommended for initial management of nephrotic syndrome. However, continued care of these children is always a collaborative effort between the nephrologist and the primary care physician.

**Etiology**

Most children with nephrotic syndrome have a form of primary or idiopathic nephrotic syndrome (Table 527-1). Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy (Table 527-2). These etiologies have different age distributions (Fig. 527-1). Nephrotic syndrome may also be secondary to systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria) (see Table 527-1). A number of hereditary proteinuria syndromes are caused by mutations in genes that encode critical protein components of the glomerular filtration apparatus (Table 527-3).

**PATHOGENESIS**

**Role of the Podocyte**

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The podocyte plays a crucial role in the development of proteinuria and progression of glomerulosclerosis. The podocyte is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop (see Chapter 508.1). Foot processes are extensions of the podocyte that terminate on the glomerular basement membrane. The foot processes of a podocyte interdigitate with those from adjacent podocytes and are connected by a slit called the slit diaphragm. The podocyte functions as structural support of the capillary loop, is a major component of the glomerular filtration barrier to proteins, and is involved in synthesis and repair of the glomerular basement membrane. The slit diaphragm is one of the major impediments to protein permeability across the glomerular capillary wall. Slit diaphragms are not simple passive filters—they consist of numerous proteins that contribute to complex signaling pathways and play an important role in podocyte function. Important component proteins of the slit diaphragm include nephrin, podocin, CD2AP, and α-actinin 4. Podocyte injury or genetic mutations of genes producing podocyte proteins may cause nephrotic-range proteinuria (see Table 527-3).

In idiopathic, hereditary, and secondary forms of nephrotic syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein “leakiness” across the glomerular capillary wall into the urinary space.

**Role of the Immune System**

Minimal change nephrotic syndrome (MCNS) may occur after viral infections and allergen challenges. MCNS has also been found to occur in children with Hodgkin lymphoma and T-cell lymphoma. That immunosuppression occurs with drugs such as corticosteroids and cyclosporine provides indirect additional evidence that the immune system contributes to the overall pathogenesis of the nephrotic syndrome.

**Clinical Consequences of Nephrotic Syndrome**

**Edema**

Edema is the most common presenting symptom of children with nephrotic syndrome. Despite its almost universal presence, there is uncertainty as to the exact mechanism of edema formation. There are 2 opposing theories, the underfill hypothesis and the overfill hypothesis, that have been proposed as mechanisms causing nephrotic edema.

The underfill hypothesis is based on the fact that nephrotic-range proteinuria leads to a fall in the plasma protein level with a corresponding decrease in intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, generating edema. As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, result in increased sodium and water retention by the tubules. Sodium and water retention therefore occur as a consequence of intravascular volume depletion.

This hypothesis does not fit the clinical picture of some patients with edema caused by nephrotic syndrome who have clinical signs of intravascular volume overload, not volume depletion. Treating these patients with albumin alone may not be sufficient to induce a diuresis.
The overfill hypothesis postulates that nephrotic syndrome is associated with primary sodium retention, with subsequent volume expansion and leakage of excess fluid into the interstitium. There is accumulating evidence that the epithelial sodium channel in the distal tubule may play a key role in sodium reabsorption in nephrotic syndrome. The clinical weaknesses of this hypothesis are evidenced by the numerous nephrotic patients who present with an obvious clinical picture of intravascular volume depletion: low blood pressure, tachycardia, and elevated hemocentration. Furthermore, amiloride, an epithelial sodium channel blocker, used alone is not sufficient to induce adequate diuresis.

The goal of therapy should be a gradual reduction of edema with judicious use of diuretics, sodium restriction, and cautious use of intravenous albumin infusions, if indicated.

Hyperlipidemia

There are several alterations in the lipid profile in children with nephrotic syndrome, including an increase in cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoproteins. The high-density lipoprotein level remains unchanged or is low. In adults, this results in an increase in the adverse cardiovascular risk ratio, although the implications for children are not as serious, especially those with steroid-responsive nephrotic syndrome. Hyperlipidemia is thought to be the result of increased synthesis as well as decreased catabolism of lipids. Although commonplace in adults, the use of lipid-lowering agents in children is uncommon.

Increased Susceptibility to Infections

Children with nephrotic syndrome are especially susceptible to infections such as cellulitis, spontaneous bacterial peritonitis, and bacteremia. This occurs as a result of many factors, particularly hyperglobulinemia as a result of the urinary losses of immunoglobulin (Ig) G. In addition, defects in the complement cascade from urinary loss of complement factors (predominantly C3 and C5), as well as alternative pathway factors B and D, lead to impaired opsonization of microorganisms. Children with nephrotic syndrome are at significantly increased risk for infection with encapsulated bacteria and, in particular, pneumococcal disease. Spontaneous bacterial peritonitis presents with fever, abdominal pain, and peritoneal signs. Although Pneumococcus is the most frequent cause of peritonitis, Gram-negative bacteria also are associated with a significant number of cases. Children with nephrotic syndrome and fever or other signs of infection must be evaluated aggressively, with appropriate cultures drawn, and should be treated promptly and empirically with antibiotics. Peritoneal leukocyte counts >250 are highly suggestive of spontaneous bacterial peritonitis.

Hypercoagulability

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors: vascular stasis from hemococoncentration and intravascular volume depletion, increased platelet number and aggregability, and changes in coagulation factor levels. There is an increase in hepatic production of fibrinogen along with urinary losses of antithrombotic...
Nephrotic Syndrome

Associated with primary glomerular disease without an identifiable causative disease or drug. Idiopathic nephrotic syndrome includes multiple histologic types: minimal change disease, mesangial proliferation, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis.

PATHOLOGY

In minimal change nephrotic syndrome (MCNS) (approximately 85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix. Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy.

Table 527-2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>MINIMAL CHANGE NEPHROTIC SYNDROME</th>
<th>FOCAL SEGMENTAL GLOMERULOSCLEROSIS</th>
<th>MEMBRANOUS NEPHROPATHY</th>
<th>MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEMOGRAPHICS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>2-6, some adults</td>
<td>2-10, some adults</td>
<td>40-50</td>
<td>5-15</td>
</tr>
<tr>
<td>Sex</td>
<td>2:1 male</td>
<td>2:1 male</td>
<td>2:1 male</td>
<td>Male-female</td>
</tr>
<tr>
<td>CLINICAL MANIFESTATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>100%</td>
<td>90%</td>
<td>80%</td>
<td>60%*</td>
</tr>
<tr>
<td>Asymptomatic proteinuria</td>
<td>0</td>
<td>10%</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>Hematuria (microscopic or gross)</td>
<td>10-20%</td>
<td>60-80%</td>
<td>60%</td>
<td>80%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10%</td>
<td>20% early</td>
<td>Infrequent</td>
<td>35%</td>
</tr>
<tr>
<td>Rate of progression to renal failure</td>
<td>Does not progress</td>
<td>10 yr</td>
<td>50% in 10-20 yr</td>
<td>10-20 yr</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>Usually none</td>
<td>HIV, heroin use, sickle cell disease, reflux nephropathy</td>
<td>Renal vein thrombosis; medications; SLE; hepatitides B, C; lymphoma; tumors</td>
<td>None</td>
</tr>
<tr>
<td>GENETICS</td>
<td>None except in congenital nephrotic syndrome (see Table 527-3)</td>
<td>Podocin, α-actinin 4, TRPC6 channel, INF-2, MYH-9</td>
<td>None</td>
<td>None</td>
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<tr>
<td>LABORATORY FINDINGS</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Manifestations of nephrotic syndrome</td>
<td>↑ BUN in 15-30%</td>
<td>Normal complement levels</td>
<td>Manifestations of nephrotic syndrome</td>
<td>Normal, complement levels—C1, C4, C3-C9</td>
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<tr>
<td>Renal pathology</td>
<td>Light microscopy</td>
<td>Normal</td>
<td>Thickened GBM, spikes</td>
<td>Thickened GBM, proliferation</td>
</tr>
<tr>
<td>Immunofluorescence</td>
<td>Negative</td>
<td>IgM, C3 in lesions</td>
<td>Fine granular IgG, C3</td>
<td>Granular IgG, C3</td>
</tr>
<tr>
<td>Electron microscopy</td>
<td>Foot process fusion</td>
<td>Foot process fusion</td>
<td>Subepithelial deposits</td>
<td>Mesangial and subendothelial deposits</td>
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<tr>
<td>REMISSION ACHIEVED AFTER 8 WK OF ORAL CORTICOSTEROID THERAPY</td>
<td>90%</td>
<td>Resistant</td>
<td>Not established/ resistant</td>
<td>Not established/ resistant</td>
</tr>
</tbody>
</table>

*Approximate frequency as a cause of idiopathic nephrotic syndrome. Approximately 10% of cases of adult nephrotic syndrome are a result of various diseases that usually manifest as acute glomerulonephritis.

†, Elevated; BUN, blood urea nitrogen; C, complement; GBM, glomerular basement membrane; Ig, immunoglobulin; SLE, systemic lupus erythematosus.


Factors such as antithrombin III and protein S. Deep venous thrombosis may occur in any venous bed, including the cerebral venous sinus, renal vein, and pulmonary veins. The clinical risk is low in children (2-5%) compared to adults, but has the potential for serious consequences.

Bibliography is available at Expert Consult.

527.1 Idiopathic Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is associated with primary glomerular disease without an identifiable causative disease or drug. Idiopathic nephrotic syndrome includes multiple histologic types: minimal change disease, mesangial proliferation, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis.
Bibliography
**Table 527-3** Nephrotic Syndrome in Children Caused by Genetic Disorders of the Podocyte

<table>
<thead>
<tr>
<th>GENE</th>
<th>NAME</th>
<th>LOCATION</th>
<th>INHERITANCE</th>
<th>RENAL DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEROID-RESISTANT</td>
<td>NPHS1 Nephrin</td>
<td>19q13.1</td>
<td>Recessive</td>
<td>Finnish-type congenital nephrotic syndrome</td>
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<tr>
<td>NEPHROTIC SYNDROME</td>
<td>NPHS2 Podocin</td>
<td>1q25</td>
<td>Recessive</td>
<td>FSGS</td>
</tr>
<tr>
<td></td>
<td>WT1 Wilms tumor-suppressor gene</td>
<td>11p13</td>
<td>Dominant</td>
<td>Denys-Drash syndrome with diffuse mesangial sclerosis Frasier syndrome with FSGS</td>
</tr>
<tr>
<td>LMX1B LIM-homeodomain protein</td>
<td>9q34</td>
<td></td>
<td>Dominant</td>
<td>Nail-patella syndrome</td>
</tr>
<tr>
<td>SMARCAL1</td>
<td>SW1/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1</td>
<td>2q35</td>
<td>Recessive</td>
<td>Schimke immunoosseous dysplasia with FSGS*</td>
</tr>
</tbody>
</table>

*Podocyte expression of SMARCAL1 is presumptive but not yet established. Mutations in another protein, CD2-AP or NEPH1 (a novel protein structurally related to nephrin), cause congenital nephrotic syndrome in mice. A mutational variant in the CD2AP gene has been identified in a few patients with steroid-resistant nephrotic syndrome.

FSGS, focal segmental glomerulosclerosis.


Mesangial proliferation is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Immunofluorescence microscopy might reveal trace to 1+ mesangial IgM and/or IgA staining. Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

In focal segmental glomerulosclerosis (FSGS), glomeruli show lesions that are both focal (present only in a proportion of glomeruli) and segmental (localized to ≥1 intraglomerular tufts). The lesions consist of mesangial cell proliferation and segmental scarring on light microscopy (Fig. 527-2 and see Table 527-2). Immunofluorescence microscopy is positive for IgM and C3 staining in the areas of segmental sclerosis. Electron microscopy demonstrates segmental scarring of the glomerular tuft with obliteration of the glomerular capillary lumen. Similar lesions may be seen secondary to HIV infection, vesicoureteral reflux, and intravenous use of heroin and other drugs of abuse. Only 20% of patients with FSGS respond to prednisone. The disease is often progressive, ultimately involving all glomeruli, and ultimately leads to end-stage renal disease in most patients.

**Figure 527-1** Kidney biopsy results from 223 children with proteinuria referred for diagnostic kidney biopsy (Glomerular Disease Collaborative Network, J. Charles Jennette, MD, Hyunsook Chin, MS, and D.S. Gipson, 2007). C1Q, nephropathy; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; n, number of patients. (From Gipson DS, Massengill SF, Yao L, et al: Management of childhood onset nephrotic syndrome, Pediatrics 124:747–757, 2009.)

![Figure 527-1 Kidney biopsy results from 223 children with proteinuria referred for diagnostic kidney biopsy (Glomerular Disease Collaborative Network, J. Charles Jennette, MD, Hyunsook Chin, MS, and D.S. Gipson, 2007). C1Q, nephropathy; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; n, number of patients. (From Gipson DS, Massengill SF, Yao L, et al: Management of childhood onset nephrotic syndrome, Pediatrics 124:747–757, 2009.)](image)

**MINIMAL CHANGE NEPHROTIC SYNDROME Clinical Manifestations**

The idiopathic nephrotic syndrome is more common in boys than in girls (2:1) and most commonly appears between the ages of 2 and 6 yr (see Fig. 527-1). However, it has been reported as early as 6 mo of age and throughout adulthood. MCNS is present in 85-90% of patients <6 yr of age. In contrast, only 20-30% of adolescents who present for the first time with nephrotic syndrome have MCNS. The more common cause of idiopathic nephrotic syndrome in this older age group is FSGS. The incidence of FSGS may be increasing; it may be more common in African-American, Hispanic, and Asian patients.

The initial episode of idiopathic nephrotic syndrome, as well as subsequent relapses, usually follows minor infections and, uncommonly, reactions to insect bites, beestings, or poison ivy.

Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities. Nephrotic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. Anorexia, irritability, abdominal pain, and diarrhea are common. Important features of minimal change idiopathic nephrotic syndrome are the absence of hypertension and gross hematuria (the so-called nephritic features).

The differential diagnosis of the child with marked edema includes protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis, and protein malnutrition. A diagnosis other than MCNS should be considered in children <1 yr of age, with a positive
Bibliography

family history of nephrotic syndrome, and/or the presence of extrarenal findings (e.g., arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency, and gross hematuria.

Diagnosis
Recommendations for the Initial Evaluation of Children with Nephrotic Syndrome

Confirming the Diagnosis of Nephrotic Syndrome.

The diagnosis of nephrotic syndrome is confirmed by urinalysis with first morning urine protein:creatinine ratio and serum electrolytes, blood urea nitrogen, creatinine, albumin, and cholesterol levels; evaluation to rule out secondary forms of nephrotic syndrome (children ≥10 yr); complement C3 level, antinuclear antibody, double-stranded DNA and hepatitides B and C, and HIV in high-risk populations; and kidney biopsy (for children ≥12 yr, who are less likely to have MCNS).

The urinalysis reveals 3+ or 4+ proteinuria, and microscopic hematuria is present in 20% of children. A spot urine protein:creatinine ratio should be >2.0. The serum creatinine value is usually normal, but it may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume. The serum albumin level is <2.5 g/dL, and serum cholesterol and triglyceride levels are elevated. Serum complement levels are normal. A renal biopsy is not routinely performed if the patient fits the standard clinical picture of MCNS.

Treatment

Children with their first episode of nephrotic syndrome and mild to moderate edema may be managed as outpatients. Such outpatient management is not practiced in all major centers, because the time required for successful education of the family regarding all aspects of the condition can require a short period of hospitalization. The child’s parents must be able to recognize the signs and symptoms of the complications of the disease and may be taught how to use a dipstick and interpret the results to monitor for the degree of proteinuria. Tuberculosis must be ruled out prior to starting immunosuppressive therapy with corticosteroids by placing a purified protein derivative or obtaining an interferon release assay, and confirming a negative result.

Children with onset of uncomplicated nephrotic syndrome between 1 and 8 yr of age are likely to have steroid-responsive MCNS, and steroid therapy may be initiated without a diagnostic renal biopsy. Children with features that make MCNS less likely (gross hematuria, hypertension, renal insufficiency, hypocomplementemia, or age <1 yr or >12 yr) should be considered for renal biopsy before treatment.

Use of Corticosteroids to Treat Minimal Change Nephrotic Syndrome

Corticosteroids are the mainstay of therapy for MCNS. The treatment guidelines for corticosteroid use presented below are adapted from and based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on glomerulonephritis.

Treatment of Initial Episode of Nephrotic Syndrome

In children with presumed MCNS, prednisone or prednisolone should be administered as a single daily dose of 60 mg/m²/day or 2 mg/kg/day to a maximum of 60 mg daily for 4-6 wk followed by alternate-day prednisone (starting at 40 mg/m² qod or 1.5 mg/kg qod) for a period ranging from 8 wk to 5 mo, with tapering of the dose. When planning the duration of steroid therapy, the side effects of prolonged corticosteroid administration must be kept in mind.

Approximately 80-90% of children respond to steroid therapy. Response is defined as the attainment of remission within the initial 4 wk of corticosteroid therapy. Remission consists of a urine protein:creatinine ratio of <0.2 or <1+ protein on urine dipstick for 3 consecutive days. The vast majority of children who respond to prednisone therapy do so within the first 5 wk of treatment.

Managing the Clinical Sequelae of Nephrotic Syndrome

Edema. Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized. In addition to sodium restriction (<1500 mg daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously, although extreme caution should be exercised. Aggressive diuresis can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis.

When a patient has severe generalized edema with evidence of intravascular volume depletion (e.g., hypotension, hypoperfusion, tachycardia), IV administration of 25% albumin (0.5-1.0 g albumin/kg) as a slow infusion followed by furosemide (1-2 mg/kg/dose IV) is sometimes necessary. Such therapy should be used only in collaboration with a pediatric nephrologist and mandates close monitoring of volume status, blood pressure, serum electrolyte balance, and renal function. Symptomatic volume overload, with hypertension, heart failure, and pulmonary edema, is a potential complication of parenteral albumin therapy, particularly when administered as rapid infusions.

Dyslipidemia. Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to <30% of calories with saturated fat intake <10% calories. Dietary cholesterol intake should be <300 mg/day. There are insufficient data to recommend the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors routinely in children with dyslipidemia.

Infections. Families of children with nephrotic syndrome should be counseled regarding the signs and symptoms of infections such as cellulitis, peritonitis, and bacteremia. If there is suspicion of infection, a blood culture should be drawn prior to starting empiric antibiotic therapy. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a paracentesis and sent for cell count, Gram stain, and culture. The antibiotic provided must be of broad enough coverage to include Pneumococcus and Gram-negative bacteria. A 3rd-generation cephalosporin is a common choice of IV antibiotic.

Thromboembolism. Children who present with the clinical signs of thromboembolism should be evaluated by appropriate imaging studies to confirm the presence of a clot. Studies to delineate a specific underlying hypercoagulable state are recommended. Anticoagulation therapy in children with thrombotic events appears to be effective—heparin, low-molecular-weight heparin, and warfarin are therapeutic options.

Obesity and Growth. Glucocorticoids may increase the body mass index in children who are overweight when steroid therapy is initiated, and these children are more likely to remain overweight. Anticipatory dietary counseling is recommended. Growth may be affected in children who require long-term corticosteroid therapy. Steroid-sparing strategies may improve linear growth in children who require prolonged courses of steroids.

Relapse of Nephrotic Syndrome. Relapse of nephrotic syndrome is defined as a urine protein:creatinine ratio of >2 or ≥3+ protein on urine dipstick testing for 3 consecutive days. Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections. Relapses are usually treated in a manner similar to the initial episode, except that daily prednisone courses are shortened. Daily high-dose prednisone is given until the child has achieved remission, and the regimen is then switched to alternate-day therapy. The duration of alternate day therapy varies depending on the frequency of relapses of the individual child. Children are classified as infrequent relapsers or frequent relapsers, and as being steroid dependent based on the number of relapses in a 12 mo period or their inability to remain in remission following discontinuation of steroid therapy.

Steroid Resistance. Steroid resistance is defined as the failure to achieve remission after 8 wk of corticosteroid therapy. Children with steroid-resistant nephrotic syndrome require further evaluation, including a diagnostic kidney biopsy, evaluation of kidney function, and quantitation of urine protein excretion (in addition to urine dipstick testing). Steroid-resistant nephrotic syndrome is
usually caused by FSGS (80%), MCNS, or membranoproliferative glomerulonephritis.

**Implications of Steroid-Resistant Nephrotic Syndrome.** Steroid-resistant nephrotic syndrome, and specifically FSGS, is associated with a 50% risk for end-stage kidney disease within 5 yr of diagnosis if patients do not achieve a partial or complete remission. Persistent nephrotic syndrome is associated with poor patient-reported quality of life, hypertension, serious infections, and thromboembolic events. Children reaching end-stage kidney disease have a greatly reduced life expectancy compared to their peers.

**Alternative Therapies to Corticosteroids in the Treatment of Nephrotic Syndrome.** Steroid-dependent patients, frequent relapsers, and steroid-resistant patients are candidates for alternative therapies, particularly if they have severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure). Cyclophosphamide prolongs the duration of remission and reduces the number of relapses in children with **frequently relapsing** and **steroid-dependent** nephrotic syndrome. The potential side effects of the drug (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy) should be carefully reviewed with the family before initiating treatment. Cyclophosphamide (2 mg/kg) is given as a single oral dose for a total duration of 8-12 wk. Alternate-day prednisone therapy is often continued during the course of cyclophosphamide administration. During cyclophosphamide therapy, the white blood cell count must be monitored weekly and the drug should be withheld if the count falls below 5,000/mm³. The cumulative threshold dose above which oligosperma or azoosperma occurs in boys is >250 mg/kg.

Calcineurin inhibitors (cyclosporine or tacrolimus) are recommended as initial therapy for children with steroid-resistant nephrotic syndrome. Children must be monitored for side effects, including hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia. Mycophenolate can maintain remission in children with steroid-dependent or frequently relapsing nephrotic syndrome. Levamisole, an anthelmintic agent with immunomodulating effects that has been shown to reduce the risk of relapse in comparison to prednisone, is not available in the United States. There are also uncontrolled preliminary data regarding prolonged remissions achieved with rituximab, the chimeric monoclonal antibody against CD20, in children with steroid-dependent and/or steroid-resistant nephrotic syndrome. There are no data from randomized clinical trials directly comparing the various corticosteroid-sparing agents. Most children who respond to cyclosporine, tacrolimus, or mycophenolate therapy tend to relapse when the medication is discontinued. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be helpful as adjunct therapy to reduce proteinuria in steroid-resistant patients.

**Immunizations in Children with Nephrotic Syndrome.** To reduce the risk of serious infections in children with nephrotic syndrome, give full pneumococcal vaccination (with the 13-valent conjugate vaccine and 23-valent polysaccharide vaccine) and influenza vaccination annually to the child and their household contacts; defer vaccination with live vaccines until the prednisone dose is below 1 mg/kg daily or 2 mg/kg on alternate days. Live virus vaccines are contraindicated in children receiving corticosteroid-sparing agents such as cyclophosphamide or cyclosporine. Following close contact with varicella infection, give immunocompromised children on immunosuppressive agents varicella-zoster immune globulin if available; immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child, but avoid direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts for 3-6 wk after vaccination.

Table 527-4 provides monitoring recommendations for children with nephrotic syndrome.

**Prognosis**

Most children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older. Although there is no proven way to predict an individual child’s course, children who respond rapidly to steroids and those who have no relapses during the first 6 mo after diagnosis are likely to follow an infrequently relapsing course. It is important to indicate to the family that the child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease, that the disease is rarely hereditary, and that the child (in the absence of prolonged cyclophosphamide therapy) will remain fertile. To minimize the psychologic

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**Table 527-4 Monitoring Recommendations for Children with Nephrotic Syndrome**

<table>
<thead>
<tr>
<th>Disease and Treatment</th>
<th>Home Urine Protein</th>
<th>Weight, Growth, BMI</th>
<th>Blood Pressure</th>
<th>Creatinine</th>
<th>Electrolytes</th>
<th>Serum Glucose</th>
<th>CBC</th>
<th>Lipid Profile</th>
<th>Drug Levels</th>
<th>Liver Function</th>
<th>Urinalysis</th>
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<td>Mild (steroid responsive)</td>
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<td>Moderate (frequent relapsing, steroid dependent)</td>
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<td>Severe (steroid resistant)</td>
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<td>Calcineurin inhibitors (cyclosporine or tacrolimus)</td>
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<tr>
<td>HMG-CoA reductase inhibitors</td>
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</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CBC, complete blood count; CPK, creatine phosphokinase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

Bibliography
effects of the condition and its therapy, children with idiopathic nephrotic syndrome should not be considered chronically ill and should participate in all age-appropriate childhood activities and maintain an unrestricted diet when in remission. Children with steroid-resistant nephrotic syndrome, most often caused by FSGS, generally have a much poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end-stage renal disease requiring dialysis or kidney transplantation. Recurrent nephrotic syndrome develops in 30-50% of transplant recipients with FSGS.

Bibliography is available at Expert Consult.

527.2 Secondary Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Nephrotic syndrome can occur as a secondary feature of many forms of glomerular disease. Membranous nephropyathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, and Henoch-Schönlein purpura nephritis can all have a nephrotic component (see Tables 527-1 and 527-2). Secondary nephrotic syndrome should be suspected in patients >8 yr and those with hypertension, hematuria, renal dysfunction, extrarenal symptoms (rash, arthralgias, fever), or depressed serum complement levels. In certain areas of the world, malaria and schistosomiasis are the leading causes of nephrotic syndrome. Other infectious agents associated with nephrotic syndrome include hepatitis B virus, hepatitis C virus, filaria, leprosy, and HIV.

Nephrotic syndrome has been associated with malignancy, particularly in the adult population. In patients with solid tumors, such as carcinomas of the lung and gastrointestinal tract, the renal pathology often resembles membranous glomerulopathy. Immune complexes composed of tumor antigens and tumor-specific antibodies presumably mediate the renal involvement. In patients with lymphomas, particularly Hodgkin lymphoma, the renal pathology most often resembles MCNS. The proposed mechanism of the nephrotic syndrome is that the lymphoma produces a lymphokine that increases permeability of the glomerular capillary wall. Nephrotic syndrome can develop before or after the malignancy is detected, resolve as the tumor regresses, and return if the tumor recurs.

Nephrotic syndrome has also developed during therapy with numerous drugs and chemicals. The histologic picture can resemble membranous glomerulopathy (penicillamine, captopril, gold, nonsteroidal antiinflammatory drugs, mercury compounds), MCNS (probenecid, ethosuximide, methimazole, lithium), or proliferative glomerulonephritis (procainamide, chlorpromazine, phenytoin, trimethadione, paramethadione).

Bibliography is available at Expert Consult.

527.3 Congenital Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Nephrotic syndrome (massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia) has a poorer prognosis when it occurs in the 1st yr of life, when compared to nephrotic syndrome manifesting in childhood. Congenital nephrotic syndrome is defined as nephrotic syndrome manifesting at birth or within the 1st 3 mo of life. Congenital nephrotic syndrome may be classified as primary or as secondary to a number of etiologies such as in utero infections (cytomegalovirus, toxoplasmosis, syphilis, hepatitis B and C, HIV), infantile systemic lupus erythematosus, or mercury exposure.

Primary congenital nephrotic syndrome is due to a variety of syndromes inherited as autosomal recessive disorders (see Table 527-3). A number of structural and functional abnormalities of the glomerular filtration barrier causing congenital nephrotic syndrome have been elucidated. In a large European cohort of children with congenital nephrotic syndrome, 85% carried disease-causing mutations in 4 genes (NPHS1, NPHS2, WT1, and LAMB2), the first 3 of which encode components of the glomerular filtration barrier. The Finnish type of congenital nephrotic syndrome is caused by mutations in the NPHS1 or NPHS2 gene, which encodes nephrin and podocin, critical components of the slit diaphragm. Affected infants most commonly present at birth with edema caused by massive proteinuria, and they are typically delivered with an enlarged placenta (>25% of the infant's weight). Severe hypoalbuminemia, hyperlipidemia, and hypogammaglobulinemia result from loss of filtering selectivity at the glomerular filtration barrier. Prenatal diagnosis can be made by the presence of elevated maternal and amniotic ß-fetoprotein levels.

Denys-Drash syndrome is caused by mutations in the WT1 gene, which results in abnormal podocyte function. Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumors.

Mutations in the LAMB2 gene, seen in Pierson syndrome, lead to abnormalities of ß-laminin, a critical component of glomerular and ocular basement membranes. In addition to congenital nephrotic syndrome, affected infants display bilateral microcoria (fixed narrowing of the pupil).

Regardless of the etiology of congenital nephrotic syndrome, diagnosis is made clinically in newborns or infants who demonstrate severe generalized edema, poor growth and nutrition with hypoalbuminemia, increased susceptibility to infections, hypothyroidism (from urinary loss of thyroxin-binding globulin), and increased risk of thrombolic events. Most infants have progressive renal insufficiency.

Secondary congenital nephrotic syndrome can resolve with treatment of the underlying cause, such as syphilis (Table 527-5). The management of primary congenital nephrotic syndrome includes intensive supportive care with intravenous albumin and diuretics, regular administration of intravenous ß-globulin, and aggressive nutritional support (often parenteral), while attempting to pharmacologically decrease urinary protein loss with angiotensin-converting enzyme.

**Table 527-5 Causes of Nephrotic Syndrome in Infants Younger Than 1 Year**

<table>
<thead>
<tr>
<th>SECONDARY CAUSES</th>
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<tbody>
<tr>
<td>Infections</td>
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<td>Syphilis</td>
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<td>Cytomegalovirus</td>
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<td>Toxoplasmosis</td>
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<td>Rubella</td>
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<td>Hepatitis B</td>
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<td>HIV</td>
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<td>Malaria</td>
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<td>Drug reactions</td>
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<td>Toxins</td>
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<tr>
<td>Mercury</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<th>Syndromes with associated renal disease</th>
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<tbody>
<tr>
<td>Syphilis-associated renal disease</td>
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<tr>
<td>Nephritis-associated renal disease</td>
</tr>
<tr>
<td>Nephritis-associated congenital renal disease</td>
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<tr>
<td>Lowe syndrome</td>
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<tr>
<td>Nephrotic syndrome with congenital brain malformation</td>
</tr>
<tr>
<td>Denys-Drash syndrome: Wilms tumor</td>
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<tr>
<td>Membranous nephropathy</td>
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</table>

inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors, or even unilateral nephrectomy. If conservative management fails and patients suffer from persistent anasarca or repeated severe infections, bilateral nephrectomies are performed and chronic dialysis is initiated. Renal transplantation is the definitive treatment of congenital nephrotic syndrome, though recurrence of the nephrotic syndrome has been reported to occur after transplantation.

*Bibliography is available at Expert Consult.*
Bibliography
SODIUM
Sodium is essential in maintaining extracellular fluid balance and, thus, volume status. The kidney is capable of effecting large changes in sodium excretion in a variety of normal and pathologic states.

There are 4 main sites of sodium transport. Approximately 60% of sodium is absorbed in the proximal tubule by coupled transport with glucose or amino acids, 25% in the ascending loop of Henle (mediated by NKCC2, the bumetanide-sensitive sodium-potassium 2 chloride transporter), and 15% in the distal tubule (mediated by NCCT, the thiazide-sensitive sodium chloride cotransporter) and collecting tubule (mediated by ENaC, the epithelial sodium channel).

The urinary excretion of sodium normally approximates the sodium intake of 2–6 mEq/kg/24 hr for a child consuming a typical American diet, minus 1–2 mEq/kg/24 hr required for normal metabolic processes. However, in states of volume depletion (dehydration, blood loss) or decreased effective circulating blood volume (septic shock, hypoaalbuminemic states, heart failure), there may be a dramatic decrease in urinary sodium excretion to as low as 1 mEq/L. Changes in systemic volume status are detected by (1) baroreceptors in the atra, afferent arteriole, and carotid sinus and (2) by the macula densa, which detects changes in chloride delivery.

The major hormonal mechanisms mediating sodium balance include the renin–angiotensin–aldosterone axis, atrial natriuretic factor, and norepinephrine. Angiotensin II and aldosterone increase sodium reabsorption in the proximal tubule and distal tubule, respectively. Norepinephrine, released in response to volume depletion, does not directly act on tubular transport mechanisms but affects sodium balance by decreasing renal blood flow, thus decreasing the filtered load of sodium as well as stimulating renin release. With more severe volume depletion, antidiuretic hormone is also released (see Chapter 530). Sodium excretion is promoted by atrial natriuretic factor and suppression of renin.

POTASSIUM
Extracellular potassium homeostasis is regulated because small changes in plasma potassium concentrations have dramatic effects on cardiac, neural, and neuromuscular function (see Chapter 55.4). Essentially, all filtered potassium is fully reabsorbed in the proximal tubule. Therefore, urinary excretion of potassium is completely dependent on tubular secretion by potassium channels present in the principal cells of the collecting tubule. Factors that promote potassium secretion include aldosterone, increased sodium delivery to the distal nephron, and increased urine flow rate.

CALCIUM
A significant portion of filtered calcium (70%) is reabsorbed in the proximal tubule. Additional calcium is reabsorbed in the ascending loop of Henle (20%) and the distal tubule and collecting duct (5–10%). Calcium is reabsorbed by passive movement between cells (paracellular absorption) in a process driven by sodium chloride reabsorption and potassium recycling into the lumen. In addition, calcium uptake is actively regulated by calcium receptors, specific transporters, and calcium channels. Factors that promote calcium reabsorption include parathyroid hormone (released in response to hypocalcemia), calcitonin, vitamin D, thiazide diuretics, and volume depletion (see Chapter 570). Factors that promote calcium excretion include volume expansion, increased sodium intake, and diuretics such as mannitol and furosemide.

PHOSPHATE
The majority of filtered phosphate is reabsorbed in the proximal tubule by active transport. Reabsorption is increased by dietary phosphorus restriction, volume contraction, and growth hormone. Parathyroid hormone and volume expansion increase phosphate excretion.

MAGNESIUM
Approximately 25% of filtered magnesium is reabsorbed in the proximal tubule. Modulation of renal magnesium excretion occurs primarily in the ascending loop of Henle, with some contribution of the distal convoluted tubule. Although specific magnesium transporters have been identified, the precise mechanisms by which they are regulated remain unclear.

ACIDIFICATION AND CONCENTRATING MECHANISMS
Acidification and concentration are addressed in the sections on renal tubular acidosis and nephrogenic diabetes insipidus, respectively (see Chapters 529 and 530).

DEVELOPMENTAL CONSIDERATIONS
Tubular transport capabilities of neonates (especially premature infants) and young infants are less than those of adults. Although nephrogenesis (the formation of new glomerular/tubular units) is complete by about 36 wk of gestation, significant tubular maturation occurs during infancy. Renal tubular immaturity, reduced glomerular filtration rate, decreased concentrating gradient, and diminished responsiveness to antidiuretic hormone are characteristic of young infants. These factors can contribute to impaired regulation of water, solute, and electrolyte and acid–base homeostasis, particularly during times of acute illness.

Bibliography is available at Expert Consult.
Bibliography

Renal tubular acidosis (RTA) is a disease state characterized by a normal anion gap (hyperchloremic) metabolic acidosis in the setting of normal or near-normal glomerular filtration rate. There are 4 main types: proximal (type II) RTA, classic distal (type I) RTA, hyperkalemic (type IV) RTA, and combined proximal and distal (type III). Proximal RTA results from impaired bicarbonate reabsorption and distal RTA from failure to secrete acid. Either of these defects may be inherited and persistent from birth or acquired, as is seen more commonly in clinical practice.

**NORMAL URINARY ACIDIFICATION**

Kidneys contribute to acid–base balance by reabsorption of filtered bicarbonate (HCO₃⁻) and excretion of hydrogen ion (H⁺) produced every day. Hydrogen ion secretion from tubule cells into the lumen is key in the reabsorption of HCO₃⁻, and the formation of titratable acid (H⁺ bound to buffers such as HPO₄²⁻), and ammonium ions (NH₄⁺). Because loss of filtered HCO₃⁻ is equivalent to addition of H⁺ to the body, all filtered bicarbonate should be absorbed before dietary H⁺ can be excreted. Approximately 90% of filtered bicarbonate is absorbed in the proximal tubule, and the remaining 10% in the distal segments, mostly the thick ascending limb and outer medullary collecting tubule (Fig. 529-1). In the proximal tubule and thick ascending limb of the loop of Henle, H⁺ from water is secreted by the Na⁺-H⁺ exchanger on the luminal membrane. H⁺ combines with filtered bicarbonate resulting in the formation of H₂CO₃, which splits into water and CO₂ in the presence of carbonic anhydrase IV. CO₂ diffuses freely back into the cell, combines with OH⁻ (from H₂O) to form HCO₃⁻ in the presence of carbonic anhydrase II, and returns to the systemic circulation via a Na⁺-HCO₃⁻ cotransporter situated at the basolateral membrane of the cell. In the collecting tubule, H⁺ is secreted into lumen by H⁺ATPase (adenosine triphosphatase) and HCO₃⁻ is returned to the systemic circulation by the HCO₃⁻-Cl⁻ exchanger located on the basolateral membrane. The H⁺ secreted proximally and distally in excess of the filtered HCO₃⁻ is excreted in the urine either as titratable acid or as NH₄⁺.

### 529.1 Proximal (Type II) Renal Tubular Acidosis

**PATHOGENESIS**

Proximal RTA can be inherited and persistent from birth or occur as a transient phenomenon during infancy. Although rare, it may be primary and isolated. Proximal RTA usually occurs as a component of global proximal tubular dysfunction or Fanconi syndrome, which is characterized by low-molecular-weight proteinuria, glycosuria, phosphaturia, aminoaciduria, and proximal RTA. Table 529-1 outlines the causes of proximal RTA (pRTA) and Fanconi syndrome. Many of these causes are inherited disorders. In addition to cystinosis and Lowe syndrome, autosomal recessive and dominant pRTA are addressed further in this section. Other inherited forms of Fanconi syndrome include galactosemia (see Chapter 87.2), hereditary fructose intolerance (see Chapter 87.3), tyrosinemia (see Chapter 85.2), and Wilson disease (see Chapter 357.2). Dent disease or X-linked nephrolithiasis, is discussed in Chapter 531.3. In children, an important form of secondary Fanconi syndrome is exposure to ifosfamide, a component of many treatment regimens for Wilms tumor and other solid tumors.

**Autosomal Recessive Disease**

Isolated autosomal recessive pRTA is caused by mutations in the gene encoding the sodium bicarbonate cotransporter NBC1. It manifests with ocular abnormalities (band keratopathy, cataracts, and glaucoma, often leading to blindness), short stature, enamel defects of the teeth, intellectual impairment, and occasionally basal ganglia calcification along with pRTA. Autosomal dominant pattern of inheritance has been identified in a single pedigree with 9 members presenting with hyperchloremic metabolic acidosis, normal ability to acidify urine, normal renal function, and growth retardation.

**Cystinosis**

Cystinosis is a systemic disease caused by a defect in the metabolism of cysteine that results in accumulation of cystine crystals in most of the major organs of the body, notably the kidney, liver, eye, and brain. It occurs at an incidence of 1:100,000 to 1:200,000. In certain populations, such as French Canadians, the incidence is much higher. At least 3 clinical patterns have been described. Young children with the most severe form of the disease (infantile or nephropathic cystinosis) present in the 1st 2 yr of life with severe tubular dysfunction and growth failure. If the disease is not treated, the children develop end-stage renal disease by the end of their 1st decade. A milder form of the disease manifests in adolescents and is characterized by less-severe tubular abnormalities and a slower progression to renal failure. A benign adult form with no renal involvement also exists.

Cystinosis is caused by mutations in the CTNS gene, which encodes a novel protein, cystinosin. Cystinosin is thought to be an H⁺-driven lysosomal cystine transporter. Genotype–phenotype studies demonstrate that patients with severe nephropathic cystinosis carry mutations that lead to complete loss of cystinosin function. Patients with milder clinical disease have mutations that lead to expression of partially functional protein. Patients with nephropathic cystinosis present with clinical manifestations reflecting their pronounced tubular dysfunction and Fanconi syndrome, including polyuria and polydipsia, growth failure, and rickets. Fever, caused by dehydration or diminished sweat production, is common. Patients are typically fair skinned and blond because of diminished pigmentation. Ocular presentations include photophobia, retinopathy, and impaired visual acuity. Patients also can develop hypothyroidism, hepatosplenomegaly, and delayed sexual
Table 529-1  Common Causes of Renal Tubular Acidosis

<table>
<thead>
<tr>
<th>PROXIMAL RENAL TUBULAR ACIDOSIS</th>
<th>PROXIMAL RENAL TUBULAR ACIDOSIS</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>Sporadic Inherited</td>
<td>Intrinsic renal</td>
</tr>
<tr>
<td>• Inherited renal disease (idiopathic Fanconi)</td>
<td>• Interstitial nephritis</td>
</tr>
<tr>
<td>• Sporadic (most common)</td>
<td>• Pyelonephritis</td>
</tr>
<tr>
<td>• Autosomal dominant</td>
<td>• Transplant rejection</td>
</tr>
<tr>
<td>• Autosomal recessive</td>
<td>• Sickle cell nephropathy</td>
</tr>
<tr>
<td>• X-linked (Dent disease)</td>
<td>• Lupus nephritis</td>
</tr>
<tr>
<td>• Inherited syndromes</td>
<td>• Nephrocalcinosis</td>
</tr>
<tr>
<td>• Cystinosis</td>
<td>• Medullary sponge kidney</td>
</tr>
<tr>
<td>• Tyrosinemia type 1</td>
<td>• Urologic</td>
</tr>
<tr>
<td>• Galactosemia</td>
<td>• Obstructive uropathy</td>
</tr>
<tr>
<td>• Oculocerebral dystrophy (Lowe syndrome)</td>
<td>• Vescicoureteral reflux</td>
</tr>
<tr>
<td>• Wilson disease</td>
<td>• Hepatic</td>
</tr>
<tr>
<td>• Hereditary fructose intolerance</td>
<td>• Cirrhosis</td>
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<table>
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<tr>
<th>DISTAL RENAL TUBULAR ACIDOSIS</th>
<th>DISTAL RENAL TUBULAR ACIDOSIS</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Secondary</strong></td>
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<tr>
<td>Sporadic Inherited</td>
<td>Urologic</td>
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<tr>
<td>• Inherited renal diseases</td>
<td>• Obstructive uropathy</td>
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<tr>
<td>• Autosomal dominant</td>
<td>• Intrinsic renal</td>
</tr>
<tr>
<td>• Autosomal recessive</td>
<td>• Pyelonephritis</td>
</tr>
<tr>
<td>• Autosomal recessive with early-onset hearing loss</td>
<td>• Interstitial nephritis</td>
</tr>
<tr>
<td>• Autosomal recessive with later-onset hearing loss</td>
<td>• Systemic</td>
</tr>
<tr>
<td>• Inherited syndromes associated with type I renal tubular acidosis</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Marfan syndrome</td>
<td>• Sickle cell nephropathy</td>
</tr>
<tr>
<td>• Wilson syndrome</td>
<td>• Drugs</td>
</tr>
<tr>
<td>• Ehlers-Danlos syndrome</td>
<td>• Trimethoprim/sulfamethoxazole</td>
</tr>
<tr>
<td>• Familial hypercalciuria</td>
<td>• Angiotensin-converting enzyme inhibitors</td>
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<tr>
<td></td>
<td>• Cyclosporine</td>
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<tr>
<td></td>
<td>• Prolonged heparinization</td>
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<tr>
<td></td>
<td>• Addison disease</td>
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</table>

maturation. With progressive tubulointerstitial fibrosis, renal insufficiency is invariant.

The diagnosis of cystinosis is suggested by the detection of cystine crystals in the cornea and confirmed by measurement of increased leukocyte cystine content. Prenatal testing is available for at-risk families.

Treatment of cystinosis is directed at correcting the metabolic abnormalities associated with Fanconi syndrome or chronic renal failure. In addition, specific therapy is available with cysteamine, which binds to cystine and converts it to cysteine. This facilitates lysosomal transport and decreases tissue cystine. Oral cysteamine does not achieve adequate levels in ocular tissues, so additional therapy with cysteamine eyedrops is required. Early initiation of the drug can prevent or delay deterioration of renal function. Patients with growth failure that does not improve with cysteamine might benefit from treatment with growth hormone. Kidney transplantation is a viable option in patients with renal failure. With prolonged survival, additional complications may become evident, including central nervous system abnormalities, muscle weakness, swallowing dysfunction, and pancreatic insufficiency. It is unclear whether long-term cysteamine therapy will decrease these complications.

Lowe Syndrome

Lowe syndrome (oculocerebrorenal syndrome of Lowe) is a rare X-linked disorder characterized by congenital cataracts, mental retardation, and Fanconi syndrome. The disease is caused by mutations in the OCRL1 gene, which encodes the phosphatidylinositol polyphosphate 5-phosphatase protein. The abnormalities seen in Lowe syndrome are thought to be caused by abnormal transport of vesicles within the Golgi apparatus. Kidneys show nonspecific tubulointerstitial changes. Thickening of glomerular basement membrane and changes in proximal tubule mitochondria are also seen.
Patients with Lowe syndrome typically present in infancy with cataracts, progressive growth failure, hypotonia, and Fanconi syndrome. Significant proteinuria is common. Blindness and renal insufficiency often develop. Characteristic behavioral abnormalities are also seen, including tantrums, stubbornness, stereotypy (repetitive behaviors), and obsessions. There is no specific therapy for the renal disease or neurologic deficits. Cataract removal is generally required.

**CLINICAL MANIFESTATIONS OF PROXIMAL RENAL TUBULAR ACIDOSIS AND FANCONI SYNDROME**

Patients with isolated, sporadic, or inherited pRTA present with growth failure in the 1st yr of life. Additional symptoms can include polyuria, dehydration (from sodium loss), anorexia, vomiting, constipation, and hypotonia. Patients with primary Fanconi syndrome have additional symptoms, secondary to phosphate wasting, such as rickets. Those with systemic diseases present with additional signs and symptoms specific to their underlying disease. A non–anion gap metabolic acidosis is present. Urinalysis in patients with isolated pRTA is generally unremarkable. The urine pH is acidic (<5.5) because distal acidification mechanisms are intact in these patients. Urinary indices in patients with Fanconi syndrome demonstrate varying degrees of phosphaturia, aminoaciduria, glycosuria, uricosuria, and elevated urinary sodium or potassium. Depending on the nature of the underlying disorder, laboratory evidence of chronic renal insufficiency, including elevated serum creatinine, may be present.

### 529.2 Distal (Type I) Renal Tubular Acidosis

**PATHOGENESIS**

Distal RTA can be sporadic or inherited. It can also occur as a complication of inherited or acquired diseases of the distal tubules. Primary or secondary causes of distal RTA can result in damaged or impaired functioning of one or more transporters or proteins involved in the acidification process, including the H^+/ATPase, the HCO_3^-/Cl^- anion exchangers, or the components of the aldosterone pathway. Because of impaired hydrogen ion excretion, urine pH cannot be reduced to <5.5, despite the presence of severe metabolic acidosis. Loss of sodium bicarbonate distally, owing to lack of H^+ to bind to in the tubular lumen (see Fig. 529-1), results in increased chloride absorption and hyperchloremia. Inability to secrete H^+ is compensated by increased K^+ secretion distally, leading to hypokalemia. Hypercalciuria is usually present and can lead to nephrocalcinosis or nephrolithiasis. Chronic metabolic acidosis also impairs urinary citrate excretion. Hypocitraturia further increases the risk of calcium deposition in the tubules. Bone disease is common, resulting from mobilization of organic components from bone to serve as buffers to chronic acidosis.

**CLINICAL MANIFESTATIONS**

Distal RTA shares features with those of pRTA, including non–anion gap metabolic acidosis and growth failure; distinguishing features of distal RTA include nephrocalcinosis and hypercalciuria. The phosphate and massive bicarbonate wasting characteristic of pRTA is generally absent. Table 529-1 lists the causes of primary and secondary distal RTA. Although inherited forms are rare, 3 specific inherited forms of distal RTA have been identified, including an autosomal recessive form associated with sensorineural deafness.

Medullary sponge kidney is a relatively rare sporadic disorder in children, although not uncommon in adults. It is characterized by cystic dilation of the terminal portions of the collecting ducts as they enter the renal pyramids. Ultrasonographically, patients often have medullary nephrocalcinosis. Although patients with this condition typically maintain normal renal function through adulthood, complications include nephrolithiasis, pyelonephritis, hyperosthenuria (inability to concentrate urine), and distal RTA. Associations of medullary sponge kidney with Beckwith-Wiedemann syndrome or hemihypertrophy have been reported.

### 529.3 Hyperkalemic (Type IV) Renal Tubular Acidosis

**Rajasree Sreedharan and Ellis D. Avner**

**PATHOGENESIS**

Type IV RTA occurs as the result of impaired aldosterone production (hypoaaldosteronism) or impaired renal responsiveness to aldosterone (pseudohypoaldosteronism). Acidosis results because aldosterone has a direct effect on the H^+/ATPase responsible for hydrogen secretion. In addition, aldosterone is a potent stimulant for potassium secretion in the collecting tubule; consequently, lack of aldosterone results in hyperkalemia. This further affects acid–base status by inhibiting ammoniagenesis and, thus, H^+ excretion. Aldosterone deficiency typically occurs as a result of adrenal gland disorders such as Addison disease or some forms of congenital adrenal hyperplasia. In children, aldosterone unresponsiveness is a more common cause of type IV RTA. This can occur transiently, during an episode of acute pyelonephritis or acute urinary obstruction, or chronically, particularly in infants and children with a history of obstructive uropathy. The latter patients can have significant hyperkalemia, even in instances when renal function is normal or only mildly impaired. Rare examples of inherited forms of type IV RTA have been identified.

**CLINICAL MANIFESTATIONS**

Patients with type IV RTA can present with growth failure in the first few years of life. Polyuria and dehydration (from salt wasting) are common. Rarely, patients (especially those with pseudohypoaldosteronism type I) present with life-threatening hyperkalemia. Patients with obstructive uropathies can present acutely with signs and symptoms of pyelonephritis, such as fever, vomiting, and foul-smelling urine. Laboratory tests reveal a hyperkalemic non–anion gap metabolic acidosis. Urine may be alkaline or acidic. Elevated urinary sodium levels with inappropriately low urinary potassium levels reflect the absence of aldosterone effect.

**DIAGNOSTIC APPROACH TO RENAL TUBULAR ACIDOSIS**

The first step in the evaluation of a patient with suspected RTA is to confirm the presence of a normal anion gap metabolic acidosis, identify electrolyte abnormalities, assess renal function, and rule out other causes of bicarbonate loss such as diarrhea (see Chapter 55). Metabolic acidosis associated with diarrheal dehydration is extremely common, and acidosis generally improves with correction of volume depletion. Patients with protracted diarrhea can deplete their total-body bicarbonate stores and can have persistent acidosis despite apparent restoration of volume status. In instances where a patient has a recent history of severe diarrhea, full evaluation for RTA should be delayed for several days to permit adequate time for reconstitution of total-body bicarbonate stores. If acidosis persists beyond a few days in this setting, additional studies are indicated.

Serum electrolytes, blood urea nitrogen, calcium, phosphorus, creatinine, and pH should be obtained by venous puncture. Traumatic blood draws (such as heel-stick specimens), small volumes of blood in “adult-size” specimen collection tubes, or prolonged specimen transport time at room temperature can lead to falsely low bicarbonate levels, often in association with an elevated serum potassium value. True hyperkalemic acidosis is consistent with type IV RTA, whereas the finding of normal or low potassium suggests type I or II. The blood anion gap should be calculated using the formula \[ [\text{Na}^+] - [\text{Cl}^- + \text{HCO}_3^-] \]. Values of <12 demonstrate the absence of an anion gap. Values of >20 indicate the presence of an anion gap. If such an anion gap is found, then other diagnoses (lactic acidosis, inborn errors of
Part XXIII

TREATMENT AND PROGNOSIS

The mainstay of therapy in all forms of RTA is bicarbonate replacement. Patients with pRTA often require large quantities of bicarbonate, up to 20 mEq/kg/24 hr, in the form of sodium bicarbonate or sodium citrate solution (Bicitra or Shohl solution). The base requirement for distal RTAs is generally in the range of 2-4 mEq/kg/24 hr, although patients’ requirements can vary. Patients with Fanconi syndrome usually require phosphate supplementation. Patients with distal RTA should be monitored for the development of hypercalciuria. Those with symptomatic hypercalciuria (recurrent episodes of gross hematuria), nephrocalcinosis, or nephrolithiasis can require thiazide diuretics to decrease urine calcium excretion. Patients with type IV RTA can require chronic treatment for hyperkalemia with sodium-potassium exchange resin (Kayexalate).

Prognosis of RTA depends to a large part on the nature of any existing underlying disease. Patients with treated isolated proximal or distal RTA generally demonstrate improvement in growth, provided serum bicarbonate levels can be maintained in the normal range. Patients with systemic illness and Fanconi syndrome can have ongoing morbidity with growth failure, rickets, and signs and symptoms related to their underlying disease.

Bibliography is available at Expert Consult.

529.4 Rickets Associated with Renal Tubular Acidosis

Russell W. Chesney

Rickets may be present in primary RTA, particularly in type II or pRTA. Hypophosphatemia and phosphaturia are common in the renal tubular acids, which are also characterized by hyperchloremic metabolic acidosis, various degrees of bicarbonaturia, and, often, hypercalciuria and hyperkalaemia. Bone demineralization without overt rickets usually is detected in type I and distal RTA. This metabolic bone disease may be characterized by bone pain, growth retardation, osteopenia, and, occasionally, pathologic fractures. Although acute metabolic acidosis in vitamin D–deficient animals can impair the conversion of 25-hydroxyvitamin D (25[OH]D) to 1,25-dihydroxyvitamin D (1,25[OH]2D), resulting in reduced levels of this active metabolite, the circulating levels of 1,25(OH)2D in patients with either type of RTA are generally normal. If patients with RTA have chronic renal insufficiency, serum 1,25(OH)2D levels are reduced in relation to the degree of renal impairment.

Bone demineralization in distal RTA probably relates to dissolution of bone because the calcium carbonate in bone serves as a buffer against the metabolic acidosis due to the hydrogen ions retained by patients with RTA.

Administration of sufficient bicarbonate to reverse acidosis reverses bone dissolution and the hypercalciuria that is common in distal RTA. Proximal RTA is treated with both bicarbonate and oral phosphate supplements to heal rickets. Doses of phosphate similar to those used in familial hypophosphatemia or Fanconi syndrome may be indicated. Vitamin D is required to offset the secondary hyperparathyroidism that complicates oral phosphate therapy. Following therapy, growth in patients with type II (proximal) RTA is greater than in patients with primary Fanconi syndrome. In addition, “double osteomalacia” may be evident when patients with either type of RTA also have vitamin D deficiency.

Figure 529-2 Ultrasound examination of a child with distal RTA demonstrating medullary nephrocalcinosis.
Bibliography
Nephrogenic diabetes insipidus (NDI) is a rare congenital or, more commonly, acquired, disorder of water metabolism characterized by an inability to concentrate urine, even in the presence of antidiuretic hormone (ADH). The most common pattern of inheritance in congenital NDI is as an X-linked recessive disorder. Rarely, affected females are seen, presumably secondary to partial X-chromosome inactivation. Approximately 10% of cases of congenital NDI are inherited as autosomal dominant or recessive disorders, with males and females affected equally. The clinical phenotype of autosomal recessive forms is similar to that of the X-linked form. Secondary (acquired), either partial or complete, forms of NDI are not uncommon. They may be seen in many disorders affecting renal tubular function.
function including obstructive uropathies, acute or chronic renal failure, renal cystic diseases, interstitial nephritis, nephrocalcinosis, or toxic nephropathy caused by hypokalemia, hypercalcemia, lithium, or amphotericin B.

**PATHOGENESIS**

The ability to concentrate urine (and thus absorb water) requires the delivery of urine to the collecting tubule; an intact concentrating gradient in the renal medulla; and the ability to modulate water permeability in the collecting tubule by ADH. ADH (also called arginine vasopressin [AVP]), is synthesized in the hypothalamus and stored in the posterior pituitary. Under basal situations, the collecting tubule is impermeable to water. However, in response to increased serum osmolality (as detected by osmoreceptors in the hypothalamus) and/or severe volume depletion, ADH is released into the systemic circulation. It then binds to its receptor, vasopressin V1 (AVPR2), on the basolateral membrane of the collecting tubule cell. Binding of the hormone to its receptor activates a cyclic adenosine monophosphate–dependent cascade that results in movement of preformed water channels (aquaporin 2 [AQP2]) to the luminal membrane of the collecting duct, rendering it permeable to water.

Defects in the AVPR2 gene cause the more common X-linked form of NDI. Mutations in the AQP2 gene have been identified in patients with the rarer autosomal dominant and recessive forms. Prenatal testing is available for families at risk for X-linked NDI. Patients with secondary forms of NDI can have ADH resistance owing to defective aquaporin expression (lithium intoxication). Secondary ADH resistance usually occurs as the result of the hypertonic medullary gradient as a result of solute diuresis or tubular damage, resulting in the inability to absorb sodium or urea.

**CLINICAL MANIFESTATIONS**

Patients with congenital NDI typically present in the newborn period with massive polyuria, volume depletion, hypernatremia, and hyperthermia. Irritability and crying are common features. Constipation and poor weight gain are also seen. After multiple episodes of hypernatremic dehydration, patients can have developmental delay and mental retardation. Enuresis, caused by large urine volumes, is common. Because of the need to consume large volumes of water during the day, patients often have diminished appetite and poor food intake. However, even with adequate caloric supplementation, patients still exhibit growth abnormalities. Patients with congenital NDI also exhibit behavioral problems, including hyperactivity and short-term memory problems. Patients with the secondary form generally present later in life, primarily with hypernatremia and polyuria. Associated symptoms such as developmental delay and behavioral abnormalities are less common in this latter group.

**DIAGNOSIS**

The diagnosis is suggested in a male infant with polyuria, hypernatremia, and diluted urine. Simultaneous serum and urine osmolality measurements should be obtained. If the serum osmolality value is 290 mOsm/kg or higher with a simultaneous urine osmolality value of <290 mOsm/kg, a formal water deprivation test is not necessary. Because the differential diagnosis includes causes of central diabetes insipidus, the inability to respond to ADH (and thus the presence of NDI) should then be confirmed by the administration of vasopressin (10–20 µg intranasally) followed by serial urine and serum osmolality measurements hourly for 4 hr. In patients with possible “partial” or secondary diabetes insipidus, in whom the initial serum osmolality value may be <290 mOsm/kg, a water-deprivation test should be considered. Fluids should be withheld and urine and serum osmolalities measured periodically until the serum osmolality value is >290 mOsm/kg; vasopressin is then given as before. Criteria for premature termination of a water-deprivation test include a decrease in body weight of >3%. If NDI is confirmed or suspected, additional evaluation should include a detailed history to assess possible toxic exposures, determination of renal function by serum creatinine and blood urea nitrogen levels, and renal ultrasonography to identify obstructive uropathies or cystic disease. Because of massive urine output, patients with congenital NDI can have nonobstructive hydronephrosis of varying severity.

**TREATMENT AND PROGNOSIS**

Treatment of NDI includes maintenance of adequate fluid intake and access to free water, minimizing urine output by limiting solute load with a low-osmolar, low-sodium diet, and administering medications directed at decreasing urine output. For infants, human milk or a low-solute formula, such as Similac PM 60/40, is preferred. Most infants with congenital NDI require gastrostomy or nasogastric feedings to ensure adequate fluid administration throughout the day and night. Sodium intake in older patients should be <0.7 mEq/kg/24 hr. Thiazide diuretics (2-3 mg/kg/24 hr of hydrochlorothiazide) effectively induce sodium loss and stimulate proximal tubule reabsorption of water. Potassium-sparing diuretics, in particular, amiloride (0.3 mg/kg/24 hr in 3 divided doses), are often indicated. Patients who have an inadequate response to diuretics alone might benefit from the addition of indomethacin (2 mg/kg/24 hr), which has an additive effect in reducing water excretion in some patients. Renal function must be monitored closely in such patients because indomethacin can cause deterioration in renal function over time. Patients with secondary NDI might not require medications but should have access to free water. Such patients should have serum electrolytes and volume status monitored closely, particularly during periods of superimposed acute illnesses.

Prevention of recurrent dehydration and hypernatremia in patients with congenital NDI has significantly improved the neurodevelopmental outcome of these patients. However, behavioral issues remain a significant problem. In addition, chronic use of nonsteroidal anti-inflammatory drugs can predispose patients to renal insufficiency. Prognosis of patients with secondary NDI generally depends on the nature of the underlying disease.

*Bibliography is available at Expert Consult.*
Bibliography
Bartter syndrome is a group of disorders characterized by hypokalemic metabolic alkalosis with hypercalciuria and salt wasting (see Chapter 55) (Table 531-1). Antenatal Bartter syndrome (types I, II, and IV; also called hyperprostaglandin E syndrome) typically manifests in infancy and has a more-severe phenotype than classic Bartter syndrome (type III); perinatal onset includes maternal polyhydramnios, neonatal salt wasting, and severe episodes of recurrent dehydration. The milder
classic Bartter syndrome. A phenotypically related disease, Gitelman syndrome, has a distinct genetic defect and is discussed in Chapter 531.2 (Table 531-1). One distinct variant of antenatal Bartter syndrome is associated with sensorineural deafness (type IV).

**PATHOGENESIS**

The biochemical features of Bartter syndrome, including hypokalemic metabolic alkalosis with hypercalciumia, resemble those seen with chronic use of loop diuretics and reflect a defect in sodium, chloride, and potassium transport in the ascending loop of Henle. The loss of sodium and chloride, with resultant volume contraction, stimulates the renin–angiotensin II–aldosterone axis. Aldosterone promotes sodium uptake and potassium secretion, exacerbating the hypokalemia. It also stimulates hydrogen ion secretion distally, worsening the metabolic alkalosis. Hypokalemia stimulates prostaglandin synthesis, which further activates the renin–angiotensin II–aldosterone axis. Bartter syndrome is associated with decreased sodium, chloride, and potassium transport in the ascending loop of Henle. The biochemical features of Bartter syndrome resemble chronic use of loop diuretics, which is elevated in Bartter syndrome and low in patients with Gitelman syndrome. Hypokalemia, low parathyroid hormone levels, hypercalciumia, and uncontrolled chronic including chronic vomiting. Kidneys demonstrate hyperplasia of the juxtaglomerular apparatus. Renal biopsy is rarely performed to diagnose this condition.

**TREATMENT AND PROGNOSIS**

Treatment of Bartter syndrome is directed at preventing dehydration, maintenance of normal serum levels of potassium, and correcting hypokalemia. Potassium supplementation, often at very high doses, is required; potassium-sparing diuretics may be of value. Even with appropriate therapy, serum potassium values might not normalize, particularly in patients with the neonatal form. Infants and young children require a high-sodium diet and at times sodium supplementation. Indomethacin, a prostaglandin inhibitor, can also be effective. If hypomagnesemia is present, magnesium supplementation is required.

**CLINICAL MANIFESTATIONS**

A history of maternal polyhydramnios with or without prematurity may be elicited. Dysmorphic features, including triangular facies, protruding ears, large eyes with strabismus, and drooping mouth may be present on physical examination. Consanguinity suggests the presence of an autosomal recessive disorder. Older children have a history of recurrent episodes of polyuria with dehydration, failure to thrive, nonspecific fatigue, dizziness, and chronic constipation. Older children may also present with muscle cramps and weakness secondary to chronic hypokalemia. Blood pressure is usually normal, although patients with the antenatal form can have severe salt wasting, resulting in dehydration and hypotension. Serum chemistry reveals the classic biochemical abnormalities of a hypokalemic metabolic alkalosis. Renal function is typically normal. Urinary calcium levels are typically elevated, as are urinary potassium and sodium levels. Serum renin, aldosterone, and prostaglandin E levels are often markedly elevated, particularly in the more-severe antenatal form. Nephrocalcinosis, resulting from hypercalcemia, may be seen on ultrasound examination (types I and II).

**DIAGNOSIS**

The diagnosis is usually made based on clinical presentation and laboratory findings. The diagnosis in the neonate or infant is suggested by severe hypokalemia, usually <2.5 mmol/L, with metabolic alkalosis. Hypercalcemia is typical; hypomagnesemia is seen in a minority of patients but is more common in Gitelman syndrome. Because features of Bartter syndrome resemble chronic use of loop diuretics, diuretic abuse should be considered in the differential diagnosis, even in young children. Chronic vomiting can also give a similar clinical picture but can be distinguished by measurement of urinary chloride, which is elevated in Bartter syndrome and low in patients with chronic vomiting.
531.2 Gitelman Syndrome

Rajasree Sreedharan and Ellis D. Avner

Gitelman syndrome (often called a “Bartter syndrome variant”) is a rare autosomal recessive cause of hypokalemic metabolic alkalosis, with distinct features of hypocalciuria and hypomagnesemia. Patients with Gitelman syndrome typically present in late childhood or early adulthood (see Table 531-1).

**PATHOGENESIS**

The biochemical features of Gitelman syndrome resemble those of chronic use of thiazide diuretics. Thiazides act on the sodium chloride cotransporter NCCT, present in the distal convoluted tubule. Through linkage analysis and mutational studies, defects in the gene encoding NCCT have been demonstrated in patients with Gitelman syndrome.

**CLINICAL MANIFESTATIONS**

Patients with Gitelman syndrome typically present at a later age than those with Bartter syndrome and may have symptoms similar to older children with Bartter syndrome (see Chapter 531.1). Patients often have a history of recurrent muscle cramps and spasms, presumably caused by low serum magnesium levels, nocturia, polyuria, and occasional hypotension. They usually do not have a history of recurrent episodes of dehydration. Biochemical abnormalities include hypokalemia, metabolic alkalosis, and hypomagnesemia. The urinary calcium level is usually very low (in contrast to the elevated urinary calcium level often seen in Bartter syndrome), and the urinary magnesium level is elevated. Renin and aldosterone levels are usually normal, and prostaglandin E secretion is not elevated. Growth failure is less prominent in Gitelman syndrome than in Bartter syndrome.

**DIAGNOSIS**

The diagnosis of Gitelman syndrome is suggested in an adolescent or adult presenting with hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria.

**TREATMENT**

Therapy is directed at correcting hypokalemia and hypomagnesemia with supplemental potassium and magnesium. Sodium supplementation or treatment with prostaglandin inhibitors is generally not necessary because patients typically do not have episodes of volume depletion or elevated prostaglandin E excretion.

531.3 Other Inherited Tubular Transport Abnormalities

Rajasree Sreedharan and Ellis D. Avner

Inherited abnormalities in distinct transporters in each segment of the nephron have now been identified and the molecular defects have been characterized. Renal tubular acidosis and nephrogenic diabetes insipidus are discussed in detail in Chapters 529 and 530, respectively. Cystinuria is an autosomal recessive disorder seen primarily in patients of Middle Eastern descent and is characterized by recurrent stone formation. The disease is caused by a defective high-affinity transporter for l-cystine and dibasic amino acids present in the proximal tubule.

Dent disease is an X-linked proximal tubulopathy with characteristic abnormalities that include low-molecular-weight proteinuria, hypercalciuria, and other features of Fanconi syndrome, such as glycosuria, aminoaciduria, and phosphaturia. Although some patients develop nephrocalcinosis, nephrolithiasis, progressive renal failure, and hypophosphatemic rickets, patients with Dent disease typically do not have proximal renal tubular acidosis or extrarenal manifestations. Loss-of-function mutations of the CLCN5 gene, which is located in Xp11.22 and encodes a renal Cl/H+ antiporter (CIC-5), are reported in patients with Dent disease. Genetic heterogeneity of Dent disease in some patients who exhibit mutations in the gene for OCRL1 (responsible for Lowe syndrome) also meets Dent disease criteria: Dent-2 disease. Dent disease includes X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemic rickets, and idiopathic low-molecular-weight proteinuria seen in Japanese children.

Mutations in an extracellular basolateral calcium-sensing receptor, normally present in the loop of Henle, can cause a dominant Bartter syndrome–like picture. These patients’ predominant symptoms are hypocalcemic and suppressed parathyroid hormone function, which differentiates them from patients with Bartter syndrome.

In the distal convoluted tubule, gain-of-function mutations in WNK1 and loss-of-function mutations in WNK4, both serine threonine kinases, lead to excessive NCCT-mediated salt reabsorption with the clinical picture of pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension, or Gordon syndrome).

In the collecting duct, gain-of-function mutations of the gene that encodes the epithelial sodium channel cause an inherited form of hypertension, Liddle syndrome. Patients with this disorder have constitutive sodium uptake in the collecting duct, with hypokalemia and suppressed aldosterone. Conversely, loss-of-function mutations cause pseudohypoaldosteronism, characterized by severe sodium wasting and hyperkalemia. A variant of the latter disorder is associated with systemic abnormalities, including defects in sweat chloride, and can resemble cystic fibrosis.

Renal hypouricemia, a defect in the SLC22A12 gene, presents with low serum uric acid levels and is complicated by exercise-induced acute renal failure. Patients have elevated urine uric acid levels and present with loin pain, nausea, and vomiting after exercise. Treatment is for acute renal failure and reducing the intensity of exercise.

*Bibliography is available at Expert Consult.*
Bibliography
Tubulointerstitial nephritis (TIN, also called interstitial nephritis) is the term applied to conditions characterized by tubulointerstitial inflammation and damage with relative sparing of glomeruli and vessels. Both acute and chronic primary forms exist. Interstitial nephritis can also be present with primary glomerular diseases as well as systemic diseases affecting the kidney.

**ACUTE TUBULOLINTERSTITIAL NEPHRITIS**

**Pathogenesis and Pathology**

The hallmarks of acute TIN are lymphocytic infiltration of the tubulointerstitium, tubular edema, and varying degrees of tubular damage. Eosinophils may be present, particularly in drug-induced TIN; occasionally, granulomas occur. The pathogenesis is not fully understood, but a T-cell–mediated immune mechanism has been postulated. A large number of medications, especially antimicrobials, anticonvulsants, and analgesics, have been implicated as etiologic agents (Table 532-1). Other causes include infections, primary glomerular diseases, and systemic diseases such as systemic lupus erythematosus.
is invariably present, but significant hematuria or proteinuria >1.5 g/day is uncommon. One exception is patients whose TIN is caused by nonsteroidal antiinflammatory drugs (NSAIDs), who can present with the nephrotic syndrome. Urinalysis can reveal white blood cell, granular, or hyaline casts, but red blood cell casts (a characteristic of glomerular disease) are absent. The presence of urine eosinophils is neither sensitive nor specific. Because of pyuria, the initial diagnosis may be a urinary tract infection.

**Diagnosis**

The diagnosis is usually based on clinical presentation and laboratory findings. A renal biopsy will establish the correct diagnosis in cases where the etiology or clinical course confounds the diagnosis. A careful history of the timing of disease onset in relation to drug exposure is essential in suspected drug-induced TIN. Because of the immune-mediated nature of TIN, signs or symptoms generally appear

**Clinical Manifestations**

The classic presentation of acute TIN is fever, rash, and arthralgia in the setting of a rising serum creatinine. Although the full triad may be noted in drug-induced TIN, many patients with acute TIN do not demonstrate all of the typical features. The rash can vary from maculopapular to urticarial and is often transient. Patients often have nonspecific constitutional symptoms of nausea, vomiting, fatigue, and weight loss. Flank pain may be present, presumably secondary to stretching of the renal capsule from acute inflammatory enlargement of the kidney. If acute TIN is caused by a systemic disease such as systemic lupus erythematosus, the clinical presentation will be consistent with specific signs and symptoms of the underlying disease. Unlike the typical presentation of oliguric acute renal failure seen with glomerular diseases, 30-40% of patients with acute TIN are nonoliguric, and hypertension is less common. Peripheral eosinophilia can occur, especially with drug-induced TIN. Some degree of microscopic hematuria

### Table 532-1  Etiology of Interstitial Nephritis

<table>
<thead>
<tr>
<th>ACUTE</th>
<th>CHRONIC</th>
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<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td><strong>Drugs and toxins</strong></td>
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<tr>
<td>Antimicrobials</td>
<td>Analgesics</td>
</tr>
<tr>
<td>Penicillin derivatives</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Lithium</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Infectious (see Acute)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Disease-associated</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Metabolic and hereditary</td>
</tr>
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<td>Vancomycin</td>
<td>Cystinosis</td>
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<tr>
<td>Erythromycin derivatives</td>
<td>Oxalosis</td>
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<tr>
<td>Rifampin</td>
<td>Fabry disease</td>
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<tr>
<td>Amphenotacin</td>
<td>Wilson disease</td>
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<tr>
<td>Acyclovir</td>
<td>Sickle cell nephropathy</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Alport syndrome</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Juvenile nephronophthisis, medullary cystic disease</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Immunologic</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>Other drugs</td>
<td>Chronic allograft rejection</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Tubulointerstitial nephritis and uveitis (TINU) syndrome</td>
</tr>
<tr>
<td>All-trans-retinoic acid</td>
<td>Antitubular basement disease</td>
</tr>
<tr>
<td>5-Aminosalicylic acid</td>
<td>Urologic</td>
</tr>
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<td>Cimetidine</td>
<td>Posterior urethral valves</td>
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<td>Cyclosporine</td>
<td>Eagle-Barrett syndrome</td>
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<td>Diuretics</td>
<td>Ureteropelvic junction obstruction</td>
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<tr>
<td>Escitalopram</td>
<td>Vesicoureteral reflux</td>
</tr>
<tr>
<td>Interferon</td>
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</tr>
<tr>
<td>Mesalazine</td>
<td>Balkan nephropathy</td>
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<tr>
<td>Quetiapine</td>
<td>Radiation</td>
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<tr>
<td>Olanzapine</td>
<td>Sarcoïdosis</td>
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<td>Nonsteroidal antiinflammatory drugs</td>
<td>Neoplasms</td>
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<tr>
<td>Protease inhibitors</td>
<td>Idiopathic</td>
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<tr>
<td>Proton pump inhibitors</td>
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within 1–2 wk following exposure. In children, antimicrobials are a common inciting agent. NSAIDs are an important cause of acute TIN in children, and volume depletion or underlying chronic renal disease can increase the risk of occurrence. Urinalysis and serial measurements of serum creatinine and electrolytes should be monitored. Renal ultrasonography is not diagnostic but can demonstrate enlarged, echogenic kidneys. Removal of a suspected offending agent followed by spontaneous improvement in renal function is highly suggestive of the diagnosis, and additional testing is generally not performed in this setting. In more severe cases, in which the cause is unclear or the patient’s renal function deteriorates rapidly, a renal biopsy is indicated.

Treatment and Prognosis
Treatment includes supportive care directed at addressing complications of acute renal failure such as hyperkalemia or volume overload (see Chapter 535.1). Corticosteroid administration within 2 wk of the discontinuation of certain offending agents (e.g., NSAIDs or antibiotics) can hasten recovery and improve the long-term prognosis in drug-induced TIN. Whether such therapy is indicated is on other causes on TIN is not clear. For patients with prolonged renal insufficiency, the prognosis remains guarded, and severe acute TIN from any cause can progress to chronic TIN.

CHRONIC TUBULOINTERSTITIAL NEPHRITIS
In children, chronic TIN most commonly occurs in the context of (1) an underlying congenital urologic renal disease, such as obstructive uropathy or vesicoureteral reflux, or (2) an underlying metabolic disorder affecting the kidneys (see Table 532–1) Chronic TIN can occur as an idiopathic disease, although this is more common in adults.

The juvenile nephronophthisis (JN)—medullary cystic kidney disease complex (MCKD) is a group of inherited, genetically determined cystic renal diseases that share the common histologic finding of chronic TIN. At least 15 different genes are associated with JN, usually inherited as an autosomal recessive disease. These genes only define 30% of cases, and new genes are being identified at a rapid pace. Although uncommon in the United States, JN causes 10–20% of pediatric end-stage renal disease (ESRD) in Europe. Patients with JN typically present with polyuria, growth failure, unexplained anemia, and chronic renal failure in late childhood or adolescence. As a ciliopathy, JN is often associated with extrarenal features such as retinal degeneration, hepatobiliary disease, cerebellar vermis hypoplasia, laterality defects, intellectual disability, and shortening of bones. These features are represented in a number of syndromes, such as Senior-Løken syndrome (retinitis pigmentosa), Joubert syndrome (cerebellar vermis hypoplasia), Bardet-Biedel syndrome (intellectual disability, obesity), and Jeune asphyxiating thoracic dystrophy (shortening of the long bones, narrow rib cage), and many others. MCKD is an autosomal dominant disease that typically manifests in adulthood.

TIN with uveitis is a rare autoimmune syndrome of chronic TIN with anterior uveitis and bone marrow granulomas that occurs primarily in adolescent girls. Chronic TIN is seen in all forms of progressive renal disease, regardless of the underlying cause, and the severity of interstitial disease is the single most important factor predicting progression to ESRD.

Pathogenesis and Pathology
The pathophysiology of chronic TIN is undefined, but data suggest that, in addition to abnormal cilia structure and function in JN and MCKD, it is immune mediated. Cells making up the interstitial infiltrate appear to be a combination of native interstitial cells, inflammatory cells recruited from the circulation, and resident tubular cells that undergo epithelial-mesenchymal transformation. Grossly, kidneys can appear pale and small for age. Microscopically, tubular atrophy and “dropout” with interstitial fibrosis and a patchy lymphocytic interstitial inflammation are seen. Patients with JN often have characteristic small cysts in the corticomedullary region. In primary chronic TIN, glomeruli are relatively spared until late in the disease course. Patients with chronic TIN secondary to a primary glomerular disease have histologic evidence of the primary disease.

Clinical Manifestations
The clinical features of chronic TIN are often nonspecific and can reflect signs and symptoms of renal insufficiency (see Chapter 535). Fatigue, growth failure, polyuria, polydipsia, and enuresis are often present. Anemia that is seemingly disproportionate to the degree of renal insufficiency is common and is a particularly prominent feature in JN. Because tubular damage often leads to renal salt wasting, significant hypertension is unusual. Fanconi syndrome, proximal renal tubular acidosis, distal renal tubular acidosis, and hyperkalemic distal renal tubular acidosis can occur.

Diagnosis
The diagnosis is suggested by signs or symptoms of renal tubular damage such as polyuria and an elevated serum creatinine value, coupled with a history suggestive of a chronic disease, such as longstanding enuresis or the presence of anemia resistant to iron therapy. Radiographic studies, in particular ultrasonography, can give additional evidence of chronicity, such as small, echogenic kidneys, corticomedullary microcysts suggesting JN, or findings of obstructive uropathy. A vesicoceystourethrogram can demonstrate the presence of vesicoureteral reflux or bladder abnormalities. If JN is suspected, molecular diagnosis is available. In instances in which the cause is unclear, a renal biopsy may be performed. In cases of advanced disease, a renal biopsy might not be diagnostic. Many end-stage kidney diseases display a common histologic appearance of tubular fibrosis and inflammation.

Treatment and Prognosis
Therapy is directed at maintaining fluid and electrolyte balance and avoiding further exposure to nephrotoxic agents. Patients with obstructive uropathies can require salt supplementation and treatment with potassium-binding resin (Kayexalate). Prevention of infection by antibiotic prophylaxis can slow progression of renal damage in appropriate patients. Prognosis in patients with chronic TIN depends in large part on the nature of the underlying disease. Patients with obstructive uropathy or vesicoureteral reflux can have a variable degree of renal damage and thus a variable course. ESRD can develop over mo to years. Patients with JN uniformly progress to ESRD by adolescence. Patients with metabolic disorders can benefit from treatment when available.

Bibliography is available at Expert Consult.
Bibliography
Aberrant renal function often results from purposeful or accidental exposure to any number of agents that are potential or actual nephrotoxins. Iodinated radiocontrast agents are generally well tolerated by most patients without significant adverse consequences. In volume-depleted patients or patients with underlying chronic kidney...
Table 533-1 Renal Syndromes Produced by Nephrotoxins

<table>
<thead>
<tr>
<th>NPHROTIC SYNDROME</th>
<th>FANCONI SYNDROME</th>
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<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Gold salts</td>
<td>Chinese herbs (aristolochic)</td>
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<tr>
<td>Interferon</td>
<td>Cisplatin</td>
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<tr>
<td>Mercury compounds</td>
<td>Heavy metals (cadmium, lead, mercury, and uranium)</td>
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<tr>
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<td>Ifosfamide</td>
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<tr>
<td>Penicillamine</td>
<td>Lysol</td>
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<tr>
<td>Neyrogenic Diabetes Insipidus</td>
<td>Outdated tetracycline</td>
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<td>Renal Tubular Acidosis</td>
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<td>Numerous other drugs that can cause a hypersensitivity reaction</td>
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<td>Oral contraceptive agents</td>
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<tr>
<td>Halothane</td>
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<tr>
<td>Heavy metals</td>
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<tr>
<td>Ifosfamide</td>
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<tr>
<td>Lithium</td>
<td></td>
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<tr>
<td>Methoxyflurane</td>
<td></td>
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<tr>
<td>Nonsteroidal antiinflammatory drugs</td>
<td></td>
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<tr>
<td>Radiographic agents</td>
<td></td>
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<tr>
<td>Tacrolimus</td>
<td></td>
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<tr>
<td>Vancomycin</td>
<td></td>
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<tr>
<td>Obstructive Uropathy</td>
<td></td>
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<tr>
<td>Sulfonamides</td>
<td></td>
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<tr>
<td>Acyclovir</td>
<td></td>
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<tr>
<td>Methotrexate</td>
<td></td>
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<tr>
<td>Protease inhibitors</td>
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<tr>
<td>Ethylene glycol</td>
<td></td>
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<tr>
<td>Methoxyflurane</td>
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</tbody>
</table>

Disease, their use poses a serious risk for the development of acute kidney injury with significant attendant morbidity and mortality. Biologic nephrotoxins include venomous exposures from insects, reptiles, amphibians, and a wide variety of sea-dwelling animals. The most common forms of toxic nephropathy unfortunately relate to the exposure of children to pharmacologic agents, accounting for close to 20% of episodes of acute kidney injury occurring in children and adolescents. Age, underlying medical condition, including surgical exposure, genetics, exposure dose, and the concomitant use of other drugs all influence the likelihood of developing acute kidney injury. Table 533-1 summarizes the agents that commonly cause acute kidney injury and some of their clinical manifestations. Mechanisms
of injury often help to explain the presentation; multiple toxic exposures in patients with complicated clinical histories often limit the ability to clearly establish clinical cause and effect. For example, diminished urine output may be the clinical hallmark of tubular obstruction caused by agents such as methotrexate or agents that cause acute tubular necrosis, such as amphotericin B or pentamidine. Alternatively, nephrogenic diabetes insipidus may be the critical clinical manifestation of agents that cause interstitial nephritis, such as lithium or cisplatin. Nephrotoxicity is often reversible if the noxious agent is promptly removed.

Clinical use of potential nephrotoxins should be used judiciously. Necessity of exposure, dosing parameters, and the use of drug levels or pharmacogenomic data, when available, should always be considered. Caution is particularly mandated for patients with complex medical conditions that include preexisting renal disease, cardiac disease, diabetes, and/or complicated surgeries. Alternative approaches to imaging, or use of different pharmacologic options should be considered when possible. Imaging modalities such as ultrasonography, radionuclide scanning, or magnetic resonance imaging may be preferable to contrast studies in some patients. Alternatively, judicious volume expansion with or without the administration of N-acetylcysteine might offer renoprotection when radioiodinated contrast studies are critical. Pharmacologic agents with no known renal effects can often be substituted for known nephrotoxins with equal clinical efficacy. In all cases, simultaneous use of known nephrotoxins should be avoided whenever necessary.

_Bibliography is available at Expert Consult._
Bibliography


Renal cortical necrosis is a rare cause of acute renal failure occurring secondary to extensive ischemic damage of the renal cortex. It occurs most commonly in neonates and in adolescents of childbearing age (see Chapter 535).

ETIOLOGY
In newborns, cortical necrosis is most commonly associated with hypoxic or ischemic insults caused by perinatal asphyxia, placental abruption, and twin–twin or fetal–maternal transfusion. Other causes include renal vascular thrombosis and severe congenital heart disease. After the neonatal period, cortical necrosis is most commonly seen in children with septic shock or severe hemolytic-uremic syndrome. In adolescents and women, cortical necrosis occurs in association with obstetric complications including prolonged intrauterine fetal death, placental abruption, or amniotic fluid embolism.

Less-common causes of cortical necrosis include malaria, extensive burns, snakebites, infectious endocarditis, and medications (e.g., non-steroidal antiinflammatory agents). Acute renal cortical necrosis has also been reported to occur in systemic lupus erythematosus–associated antiphospholipid antibody syndrome.

CLINICAL MANIFESTATIONS
Cortical necrosis clinically presents as acute renal failure in patients with predisposing causes. Urine output is diminished and gross and/or microscopic hematuria may be present. Hypertension is common, and thrombocytopenia may be present as a result of renal microvascular injury.

LABORATORY AND RADIOLOGIC FINDINGS
Laboratory results are consistent with acute renal failure: an elevated blood urea nitrogen and creatinine, hyperkalemia, and metabolic acidosis. Anemia and thrombocytopenia are common. Urinalysis reveals hematuria and proteinuria.

Ultrasound examination with Doppler flow studies or CT scan demonstrates decreased perfusion to both kidneys. A radionuclide renal scan shows decreased uptake with significantly delayed or absent function.

TREATMENT
It is important to prevent or treat the underlying cause of acute cortical necrosis, when possible. Therapy involves medical management of acute renal failure, often with the initiation of dialysis as indicated. Management is otherwise supportive and involves volume repletion, correction of asphyxia, and treatment of sepsis.

PROGNOSIS
Untreated, renal cortical necrosis has a high mortality rate. Twenty to 40% of patients have partial recovery of renal function, the extent of which depends on the amount of preserved cortical tissue. All patients require long-term follow-up for chronic kidney disease.

Bibliography is available at Expert Consult.
Bibliography


Acute kidney injury (AKI), formerly called acute renal failure, is a clinical syndrome in which a sudden deterioration in renal function results in the inability of the kidneys to maintain fluid and electrolyte homeostasis. AKI occurs in 2-3% of children admitted to pediatric tertiary care centers and in as many as 8% of infants in neonatal intensive care units. A classification system has been proposed to standardize the definition of AKI in adults. These criteria of risk, injury, failure, loss, and end-stage renal disease were given the acronym of RIFLE. A modified RIFLE criteria (pRIFLE) was developed to characterize the pattern of AKI in critically ill children (Table 535-1). Because RIFLE focuses on the glomerular filtration rate (GFR), a modification (Acute Kidney Injury Network) categorizes severity by rise in serum creatinine: stage I >150%, stage II >200%, stage III >300%.

**PATHOGENESIS**
AKI has been conventionally classified into 3 categories: prerenal, intrinsic renal, and postrenal (Table 535-2 and Fig. 535-1).

### Table 535-1
**Pediatric-Modified RIFLE (pRIFLE) Criteria**

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>ESTIMATED CCl</th>
<th>URINE OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>eCCl decrease by 25%</td>
<td>&lt;0.5 mL/kg/hr for 8 hr</td>
</tr>
<tr>
<td>Injury</td>
<td>eCCl decrease by 50%</td>
<td>&lt;0.5 mL/kg/hr for 16 hr</td>
</tr>
<tr>
<td>Failure</td>
<td>eCCl decrease by 75% or eCCl &lt;35 mL/min/1.73 m²</td>
<td>&lt;0.3 mL/kg/hr for 24 hr or anuric for 12 hr</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent failure &gt;4 wk</td>
<td></td>
</tr>
<tr>
<td>End-stage</td>
<td>End-stage renal disease (persistent failure &gt;3 mo)</td>
<td></td>
</tr>
</tbody>
</table>

CCI, creatinine clearance; eCCl, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss, and end-stage renal disease.
Prerenal AKI, also called prerenal azotemia, is characterized by diminished effective circulating arterial volume, which leads to inadequate renal perfusion and a decreased GFR. Evidence of kidney damage is absent. Common causes of prerenal AKI include dehydration, sepsis, hemorrhage, severe hypoalbuminemia, and cardiac failure. If the underlying cause of the renal hypoperfusion is reversed promptly, renal function returns to normal. If hypoperfusion is sustained, intrinsic renal parenchymal damage can develop.

Intrinsic renal AKI includes a variety of disorders characterized by renal parenchymal damage, including sustained hypoperfusion and ischemia. Many forms of glomerulonephritis, including postinfectious glomerulonephritis, lupus nephritis, Henoch-Schönlein purpura nephritis, membra noproliferative glomerulonephritis, and anti-glomerular basement membrane nephritis, can cause AKI. Ischemic/。

hypoxic injury and nephrotoxic insults are the most common causes of intrinsic AKI in the United States, and are more common with an underlying comorbid condition; most are associated with cardiac, oncologic, urologic, renal, and genetic disorders or prematurity. Severe and prolonged ischemic/hypoxic injury and nephrotoxic insult lead to acute tubular necrosis (ATN), seen most often in critically ill infants and children. Mechanisms leading to ischemic AKI include hypotension/intravascular volume depletion (hemorrhage, third-space fluid losses, diarrhea), decreased effective intravascular volume (heart failure, cirrhosis, hepatorenal syndrome, peritonitis, abdominal compartment syndrome), vasodilation/vasoconstriction (sepsis, hepatorenal syndrome), renal artery obstruction (thrombosis, embolization, stenosis), intrarenal artery disease (vasculitis, hemolytic-uremic syndrome, sickle cell anemia, transplant rejection), and impaired renal blood flow (cyclosporine, tacrolimus, angiotensin-converting enzyme [ACE] inhibitors, angiotensin-receptor blocking agents, radiocontrast agents).

The typical pathologic feature of ATN is tubular cell necrosis, although significant histologic changes are not consistently seen in patients with clinical ATN. The mechanisms of injury in ATN can include alterations in intrarenal hemodynamics, tubular obstruction, and passive backleak of the glomerular filtrate across injured tubular cells into the peritubular capillaries.

Tumor lysis syndrome is a specific form of AKI related to spontaneous or chemotherapy-induced cell lysis in patients with lymphoproliferative malignancies. This disorder is primarily caused by obstruction of the tubules by uric acid crystals (see Chapters 495 and 496). Acute interstitial nephritis is another common cause of AKI and is usually a result of a hypersensitivity reaction to a therapeutic agent or various infectious agents (see Chapter 532). Postrenal AKI includes a variety of disorders characterized by obstruction of the urinary tract. In neonates and infants, congenital conditions, such as posterior urethral valves and bilateral ureteropelvic junction obstruction, account for the majority of cases of AKI. Other conditions, such as urolithiasis, tumor (intraabdominal lesion or within the urinary tract), hemorrhagic cystitis, and neurogenic bladder, can cause AKI in older children and adolescents. In a patient with 2 functioning kidneys, obstruction must be bilateral to result in AKI. Relief of the obstruction usually results in recovery of renal function, except in patients with associated renal dysplasia or prolonged urinary tract obstruction.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

A carefully taken history is critical in defining the cause of AKI. An infant with a 3 day history of vomiting and diarrhea most likely has prerenal AKI caused by volume depletion, but hemolytic-uremic syndrome (HUS) must be a consideration. A 6 yr old child with a recent pharyngitis who presents with periorbital edema, hypertension, and gross hematuria most likely has intrinsic AKI related to acute postinfectious glomerulonephritis. A critically ill child with a history of protracted hypotension or with exposure to nephrotoxic medications most likely has ATN. A neonate with a history of hydronephrosis on prenatal ultrasound and a palpable bladder most likely has congenital urinary tract obstruction, probably related to posterior urethral valves.

The physical examination must be thorough, with careful attention to volume status. Tachycardia, dry mucous membranes, and poor peripheral perfusion suggest an inadequate circulating volume and the possibility of prerenal AKI (see Chapter 57). Hypertension, peripheral edema, rales, and a cardiac gallop suggest volume overload and the possibility of intrinsic AKI from glomerulonephritis or ATN. The presence of a rash and arthritis might indicate systemic lupus erythematosus (SLE) or Henoch-Schönlein purpura nephritis. Palpable flank masses may be seen with renal vein thrombosis, tumors, cystic disease, or urinary tract obstruction.

**LABORATORY FINDINGS**

Laboratory abnormalities can include anemia (the anemia is usually dilutional or hemolytic, as in SLE, renal vein thrombosis,
**Table 535-3  Urinalysis, Urine Chemistries, and Osmolality in Acute Kidney Injury**

<table>
<thead>
<tr>
<th>Sediment</th>
<th>HYPOVOLEMIA</th>
<th>ACUTE TUBULAR NECROSIS</th>
<th>ACUTE INTERSTITIAL NEPHRITIS</th>
<th>GLOMERULONEPHRITIS</th>
<th>OBSTRUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>None or low</td>
<td>Broad, brownish granular casts</td>
<td>White blood cells, eosinophils, cellular casts</td>
<td>Red blood cells, red blood cell casts</td>
<td>Bland or bloody</td>
</tr>
<tr>
<td>Urine sodium, mEq/L&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt;20</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&lt;20 (acute)</td>
<td>&lt;20 (acute)</td>
</tr>
<tr>
<td>Urine osmolality, mOsm/kg</td>
<td>&gt;400</td>
<td>&lt;350</td>
<td>&lt;350</td>
<td>&gt;400</td>
<td>&lt;350</td>
</tr>
<tr>
<td>Fractional excretion of sodium %&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>&gt;1</td>
<td>Varies</td>
<td>&lt;1 (acute)</td>
<td>&gt;1 (few days)</td>
</tr>
</tbody>
</table>

<sup>1</sup>The sensitivity and specificity of sodium of <20 mEq/L in differentiating prerenal azotemia from acute tubular necrosis are 90% and 82%, respectively.

<sup>2</sup>Fractional excretion of sodium is the urine:plasma (U/P) ratio of sodium divided by U/P of creatinine x100. The sensitivity and specificity of fractional excretion of sodium of <1% in differentiating prerenal azotemia from acute tubular necrosis are 96% and 95%, respectively.

NSAIDs, nonsteroidal antiinflammatory drugs.


HUS); leukopenia (SLE, sepsis); thrombocytopenia (SLE, renal vein thrombosis, sepsis, HUS); hyponatremia (dilutional); metabolic acidosis; elevated serum concentrations of blood urea nitrogen, creatinine, uric acid, potassium, and phosphate (diminished renal function); and hypocalcemia (hyperparathyroidism).

The serum C3 level may be depressed (postinfectious glomerulonephritis, SLE, or membranoproliferative glomerulonephritis), and antibodies may be detected in the serum to streptococcal (post-streptococcal glomerulonephritis), nuclear (SLE), neutrophil cytoplasmic (granulomatosis with polyangiitis, microscopic polyarteritis), or glomerular basement membrane (Goodpasture disease) antigens.

The presence of hematuria, proteinuria, and red blood cell or granular urinary casts suggests intrinsic AKI, in particular glomerular disease and ATN. The presence of white blood cells and white blood cell casts with low-grade hematuria and proteinuria suggests tubulointerstitial disease. Urinary eosinophils may be present in children with drug-induced tubulointerstitial nephritis.

Urinary indices may be useful in differentiating prerenal AKI from intrinsic AKI (Table 535-3). Patients whose urine shows an elevated specific gravity (>1.020), elevated urine osmolality (UOsm > 500 mOsm/kg), low urine sodium (UNa < 20 mEq/L), and fractional excretion of sodium <1% (<2.5% in neonates) most likely have prerenal AKI. Those with a specific gravity of <1.010, low urine osmolality (UOsm < 350 mOsm/kg), high urine sodium (UNa > 40 mEq/L), and fractional excretion of sodium >2% (>10% in neonates) most likely have intrinsic AKI.

Chest radiography may reveal cardiomegaly, pulmonary congestion (fluid overload), or pleural effusions. Renal ultrasonography can reveal hydropnephrosis and/or hydroureret, which suggest urinary tract obstruction, or nephromegaly, consistent with intrinsic renal disease. Renal biopsy can ultimately be required to determine the precise cause of AKI in patients who do not have clearly defined prerenal or postrenal AKI.

Although serum creatinine is used to measure kidney function, it is an insensitive and delayed measure of decreased kidney function following AKI. Other biomarkers under investigation include changes in plasma neutrophil gelatinase-associated lipocalin and cystatin C levels and urinary changes in neutrophil gelatinase-associated lipocalin, interleukin 18, and kidney injury molecule-1.

**TREATMENT**

**Medical Management**

In infants and children with urinary tract obstruction, such as in a newborn with suspected posterior urethral valves, a bladder catheter should be placed immediately to ensure adequate drainage of the urinary tract. The placement of a bladder catheter may also be considered in nonambulatory older children and adolescents to accurately monitor urine output during AKI; however, precautions to prevent iatrogenic infection should be taken.

Determination of the volume status is of critical importance when initially evaluating a patient with AKI. If there is no evidence of volume overload or cardiac failure, intravascular volume should be expanded by intravenous administration of isotonic saline, 20 mL/kg over 30 min. In the absence of blood loss or hypoproteinemia, colloid-containing solutions are not required for volume expansion. Severe hypovolemia may require additional fluid boluses (see Chapters 56, 57, and 70). Determination of the central venous pressure may be helpful if adequacy of the blood volume is difficult to determine. After volume resuscitation, hypovolemic patients generally void within 2 hr; failure to do so suggests intrinsic or postrenal AKI. Hypotension caused by sepsis requires vigorous fluid resuscitation followed by a continuous infusion of norepinephrine.

Diuretic therapy should be considered only after the adequacy of the circulating blood volume has been established. Furosemide (2-4 mg/kg) and mannitol (0.5 g/kg) may be administered as a single IV dose. Bumetanide (0.1 mg/kg) may be given as an alternative to furosemide. If urine output is not improved, then a continuous diuretic infusion may be considered. To increase renal cortical blood flow, many clinicians administer dopamine (2-3 µg/kg/min) in conjunction with diuretic therapy, although no controlled data support this practice. There is little evidence that diuretics or dopamine can prevent AKI or hasten recovery. Mannitol may be effective in prevention of pigment (myoglobin, hemoglobin)-induced renal failure. Atrial natriuretic peptide may be of value in preventing or treating AKI, although there is little pediatric evidence to support its use.

If there is no response to a diuretic challenge, diuretics should be discontinued and fluid restriction is essential. Patients with a relatively normal intravascular volume should initially be limited to 400 mL/m<sup>2</sup>/24 hr (insensible losses) plus an amount of fluid equal to the urine output for that day. Extrarenal (blood, gastrointestinal tract) fluid losses should be replaced, milliliter for milliliter, with appropriate fluids. Markedly hypervolemic patients can require further fluid restriction, omitting the replacement of insensible fluid losses, urine output, and extrarenal losses to diminish the expanded intravascular volume. Fluid intake, urine and stool output, body weight, and serum chemistries should be monitored on a daily basis.

In AKI, rapid development of hyperkalemia (serum potassium level > 6 mEq/L) can lead to cardiac arrhythmia, cardiac arrest, and death. The earliest electrocardiographic change seen in patients with developing hyperkalemia is the appearance of peaked T waves. This may be followed by widening of the QRS intervals, ST segment depression, ventricular arrhythmias, and cardiac arrest (see Chapter 55.4).
Procedures to deplete body potassium stores should be initiated when the serum potassium value rises to >6.0 mEq/L. Exogenous sources of potassium (dietary, intravenous fluids, total parenteral nutrition) should be eliminated. Sodium polystyrene sulfonate resin (Kayexalate), 1 g/kg, should be given orally or by retention enema. This resin exchanges sodium for potassium and can take several hr to take effect. A single dose of 1 g/kg can be expected to lower the serum potassium level by about 1 mEq/L. Resin therapy may be repeated every 2 hr, the frequency being limited primarily by the risk of sodium overload.

More severe elevations in serum potassium (>7 mEq/L), especially if accompanied by electrocardiographic changes, require emergency measures in addition to Kayexalate. The following agents should be administered:

- **Calcium gluconate** 10% solution, 1.0 mL/kg IV, over 3-5 min
- **Sodium bicarbonate**, 1-2 mEq/kg IV, over 5-10 min
- **Regular insulin**, 0.1 units/kg, with glucose 50% solution, 1 mL/kg, over 1 hr

Calcium gluconate counteracts the potassium-induced increase in myocardial irritability but does not lower the serum potassium level. Administration of sodium bicarbonate, insulin, or glucose lowers the serum potassium level by shifting potassium from the extracellular to the intracellular compartment. A similar effect has been reported with the acute administration of β-adrenergic agonists in adults, but there are no controlled data in pediatric patients. Because the duration of action of these emergency measures is just a few hours, persistent hyperkalemia should be managed by dialysis.

**Mild metabolic acidosis** is common in AKI because of retention of hydrogen ions, phosphate, and sulfate, but it rarely requires treatment. If acidosis is severe (arterial pH < 7.15; serum bicarbonate < 8 mEq/L) or contributes to significant hyperkalemia, treatment is indicated. The acidosis should be corrected partially by the intravenous route, generally giving enough bicarbonate to raise the arterial pH to 7.20 (which approximates a serum bicarbonate level of 12 mEq/L). The remainder of the correction may be accomplished by oral administration of sodium bicarbonate after normalization of the serum calcium and phosphorus levels. Correction of metabolic acidosis with intravenous bicarbonate can precipitate tetany in patients with renal failure as rapid correction of acidosis reduces the ionized calcium concentration (see Chapter 55).

**Hypocalcemia** is primarily treated by lowering the serum phosphorus level. Calcium should not be given intravenously, except in cases of tetany, to avoid deposition of calcium salts into tissues. Patients should be instructed to follow a low-phosphorus diet, and phosphate binders should be orally administered to bind any ingested phosphate and increase GI phosphate excretion. Common agents include sevelamer (Renagel), calcium carbonate (Tums tablets or Titralac suspension), and calcium acetate (PhosLo). Aluminum-based binders, commonly employed in the past, should be avoided because of the risk of aluminum toxicity.

**Hypotension** is most commonly a dilutional disturbance that must be corrected by fluid restriction rather than sodium chloride administration. Administration of hypertonic (3%) saline should be limited to patients with symptomatic hypotension (seizures, lethargy) or those with a serum sodium level <120 mEq/L. Acute correction of the serum sodium to 125 mEq/L (mmol/L) should be accomplished using the following formula:

\[
\text{mEq sodium required} = 0.6 \times \text{weight in kg} \times (125 - \text{serum sodium in mEq/L}).
\]

AKI patients are predisposed to **GI bleeding** because of uremic platelet dysfunction, increased stress, and heparin exposure if treated with hemodialysis or continuous renal replacement therapy. Oral or intravenous H₂ blockers such as ranitidine are commonly administered to prevent this complication.

**Hypertension** can result from hyperreninemia associated with the primary disease process and/or expansion of the extracellular fluid volume and is most common in AKI patients with acute glomerulonephritis or HUS. Salt and water restriction is critical, and diuretic administration may be useful (see Chapter 445). Isradipine (0.05-0.15 mg/kg/dose, maximum dose 5 mgqid) may be administered for relatively rapid reduction in blood pressure. Longer-acting agents such as calcium channel blockers (amlodipine, 0.1-0.6 mg/kg/24 hr qd or divided bid) or β blockers (propranolol, 0.5-8.0 mg/kg/24 hr divided bid or tid; labetalol, 4-40 mg/kg/24 hr divided bid or tid) may be helpful in maintaining control of blood pressure. Children with severe symptomatic hypertension (hypertensive urgency or emergency) should be treated with continuous infusions of nicardipine (0.5-5.0 µg/kg/min), sodium nitroprusside (0.5-10.0 µg/kg/min), or esmolol (150-300 µg/kg/min) and converted to intermittently dosed antihypertensives when more stable.

**Neurologic symptoms** in AKI can include headache, seizures, lethargy, and confusion (encephalopathy). Potential etiologic factors include hypertensive encephalopathy, hyponatremia, hypocalcemia, cerebral hemorrhage, cerebral vasculitis, and the uremic state. Benzodiazepams are the most effective agents in acutely controlling seizures, and subsequent therapy should be directed toward the precipitating cause.

The **anemia** of AKI is generally mild (hemoglobin 9-10 g/dL) and primarily results from volume expansion (hemodilution). Children with HUS, SLE, active bleeding, or prolonged AKI can require transfusion of packed red blood cells if their hemoglobin level falls below 7 g/dL. In hypervolemic patients, blood transfusion carries the risk of further volume expansion, which can precipitate hypertension, heart failure, and pulmonary edema. Slow (4-6 hr) transfusion with packed red blood cells (10 mL/kg) diminishes the risk of hypervolemia. The use of fresh, washed red blood cells minimizes the acute risk of hyperkalemia, and the chronic risk of sensitization if the patient becomes a future candidate for renal replacement therapy. In the presence of severe hypervolemia or hyperkalemia, blood transfusions are most safely administered during dialysis or ultrafiltration.

**Nutrition** is of critical importance in children who develop AKI. In most cases, sodium, potassium, and phosphorus should be restricted. Protein intake should be moderately restricted while maximizing caloric intake to minimize the accumulation of nitrogenous wastes. In critically ill patients with AKI, parenteral hyperalimentation with essential amino acids should be considered.

**Dialysis**

Indications for dialysis in AKI include the following:

- Anuria/oliguria
- Volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy
- Persistent hyperkalemia
- Severe metabolic acidosis unresponsive to medical management
- Uremia (encephalopathy, pericarditis, neuropathy)
- Blood urea nitrogen >100-150 mg/dL (or lower if rapidly rising)
- Calcium/phosphorus imbalance, with hypocalcemic tetany that cannot be controlled by other measures

An additional indication for dialysis is the inability to provide adequate nutritional intake because of the need for severe fluid restriction. In patients with AKI, dialysis support may be necessary for days or for up to 12 wk. Many patients with AKI require dialysis support for 1-3 wk. Table 535-4 lists the advantages and disadvantages of the 3 types of dialysis.

**Intermittent hemodialysis** is useful in patients with relatively stable hemodynamic status. This highly efficient process accomplishes both fluid and electrolyte removal in 3-4 hr sessions using a pump-driven extracorporeal circuit and large central venous catheter. Intermittent hemodialysis may be performed 3-7 times per week based on the patient's fluid and electrolyte balance.

**Peritoneal dialysis** is most commonly employed in neonates and infants with AKI, although this modality may be used in children and adolescents of all ages. Hypersmolar dialysate is infused into the peritoneal cavity via a surgically or percutaneously placed peritoneal dialysis catheter. The fluid is allowed to dwell for 45-60 min and is then drained from the patient by gravity (manually or with the use of machine-driven cycling), accomplishing fluid and electrolyte removal. Cycles are repeated for 8-24 hr/day based on the patient's fluid and electrolyte status.
fluid and electrolyte balance. Anticoagulation is not necessary. Peritoneal dialysis is contraindicated in patients with significant abdominal pathologies.

**Continuous renal replacement therapy** (CRRT) is useful in patients with unstable hemodynamic status, concomitant sepsis, or multiorgan failure in the intensive care setting. CRRT is an extracorporeal therapy in which fluid, electrolytes, and small- and medium-size solutes are continuously removed from the blood (>24 hr/day) using a specialized pump-driven machine. Usually, a double-lumen catheter is placed into the subclavian, internal jugular, or femoral vein. The patient is then connected to the pump-driven CRRT circuit, which continuously passes the patient’s blood across a highly permeable filter.

CRRT may be performed in 3 basic fashions. In continuous venovenous hemofiltration, a large volume of fluid is driven by systemic or pump-assisted pressure across the filter, bringing with it by convection other molecules such as urea, creatinine, phosphorus, and uric acid. The blood volume is reconstituted by IV infusion of a replacement fluid having a desirable electrolyte composition similar to that of blood. Continuous venovenous hemofiltration dialysis uses the principle of diffusion by circulating dialysate in a countercurrent direction on the ultrafiltrate side of the membrane. No replacement fluid is used. Continuous hemofiltration employs both replacement fluid and dialysate, offering the most effective solute removal of all forms of CRRT.

**PROGNOSIS**

The mortality rate in children with AKI is variable and depends entirely on the nature of the underlying disease process rather than on the renal failure itself. Children with AKI caused by a renal-limited condition have a very low mortality rate (<1%); those with AKI related to multiorgan failure have a very high mortality rate (>90%).

The prognosis for recovery of renal function depends on the disorder that precipitated AKI. Recovery of renal function is likely after AKI resulting from prerenal causes ATN, acute interstitial nephritis, or tumor lysis syndrome. Recovery of renal function is unusual when AKI results from most types of rapidly progressive glomerulonephritis, bilateral renal vein thrombosis, or bilateral cortical necrosis. Medical management may be necessary for a prolonged period to treat the sequelae of AKI, including chronic renal insufficiency, hypertension, renal tubular acidosis, and urinary concentrating defect.

**Bibliography is available at Expert Consult.**

### 535.2 Chronic Kidney Disease

Rajasree Sreedharan and Ellis D. Avner

Chronic kidney disease (CKD) is determined by the presence of kidney damage and level of kidney function (GFR), irrespective of diagnosis. The stage of the CKD is assigned based on the level of kidney function (Tables 535-5 and 535-6). The prevalence of CKD in the pediatric population is approximately 18 per 1 million. The prognosis for the infant, child, or adolescent with CKD has improved dramatically since the 1970s because of improvements in medical management (aggressive nutritional support, recombinant erythropoietin, recombinant growth hormone), dialysis techniques, and kidney transplantation.

**ETIOLOGY**

In children, CKD may be the result of congenital, acquired, inherited, or metabolic renal disease, and the underlying cause correlates closely with the age of the patient at the time when CKD is first detected. CKD in children <5 yr old is most commonly a result of congenital abnormalities such as renal hypoplasia, dysplasia, or obstructive uropathy. Additional causes include congenital nephrotic syndrome, prune belly syndrome, cortical necrosis, focal segmental glomerulosclerosis, autosomal recessive polycystic kidney disease, renal vein thrombosis, and HUS. After 5 yr of age, acquired diseases (various forms of glomerulonephritis including lupus nephritis) and inherited disorders (familial

### Table 535-5

<table>
<thead>
<tr>
<th>Criteria for Definition of Chronic Kidney Disease (NKF KDOQI Guidelines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient has CKD if either of the following criteria are present: 1. Kidney damage for ≥3 mo, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by 1 or more of the following features: • Abnormalities in the composition of the blood or urine • Abnormalities in imaging tests • Abnormalities on kidney biopsy 2. GFR &lt;60 mL/min/1.73 m² for ≥3 mo, with or without the other signs of kidney damage described above</td>
</tr>
</tbody>
</table>

NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

### Table 535-6

<table>
<thead>
<tr>
<th>Standardized Terminology for Stages of Chronic Kidney Disease (NKF KDOQI Guidelines)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAGE</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.
Bibliography
juvenile nephronophthisis, Alport syndrome) predominate. CKD related to metabolic disorders (cystinosis, hyperoxaluria) and certain inherited disorders (both autosomal dominant and recessive polycystic kidney disease) can occur throughout the childhood years.

**PATHOGENESIS**
In addition to progressive injury with ongoing structural or metabolic genetic diseases, renal injury can progress despite removal of the original insult.

Hyperfiltration injury may be an important final common pathway of glomerular destruction, independent of the underlying cause of renal injury. As nephrons are lost, the remaining nephrons undergo structural and functional hypertrophy characterized by an increase in glomerular blood flow. The driving force for glomerular filtration is thereby increased in the surviving nephrons. Although this compensatory hyperfiltration temporarily preserves total renal function, it can cause progressive damage to the surviving glomeruli, possibly by a direct effect of the elevated hydrostatic pressure on the integrity of the capillary wall and/or the toxic effect of increased protein traffic across the capillary wall. Over time, as the population of sclerosed nephrons increases, the surviving nephrons suffer an increased excretory burden, resulting in a vicious cycle of increasing glomerular blood flow and hyperfiltration injury.

Proteinuria itself can contribute to renal functional decline. Proteins that traverse the glomerular capillary wall can exert a direct toxic effect on tubular cells and recruit monocytes and macrophages, enhancing the process of glomerular sclerosis and tubulointerstitial fibrosis. Uncontrolled hypertension can exacerbate disease progression by causing arteriolar nephrosclerosis and by increasing the hyperfiltration injury.

Hyperphosphatemia can increase progression of disease by leading to calcium phosphate deposition in the renal interstitium and blood vessels. Hyperlipidemia, a common condition in CKD patients, can adversely affect glomerular function through oxidant-mediated injury.

CKD may be viewed as a continuum of disease, with increasing biochemical and clinical manifestations as renal function deteriorates. Regardless of etiology, the progression of tubulointerstitial fibrosis is the primary determinant of progression of CKD. Table 535-7 outlines the pathophysiologic manifestations of CKD. End-stage renal disease (ESRD) is an administrative term in the United States; it is used to define all patients who are treated with dialysis or kidney transplantation. Patients with ESRD are a subset of the patients with stage 5 CKD.

**CLINICAL MANIFESTATIONS**
The clinical presentation of CKD is varied and depends on the underlying renal disease. Children and adolescents with CKD from chronic glomerulonephritis can present with edema, hypertension, hematuria, and proteinuria. Infants and children with congenital disorders such as renal dysplasia and obstructive uropathy can present in the neonatal period with failure to thrive, polyuria, dehydration, urinary tract infection, or overt renal insufficiency. Congenital kidney disease is diagnosed with prenatal ultrasonography in many infants, allowing early diagnosis and possible therapeutic intervention. Children with familial juvenile nephronophthisis can have a very subtle presentation with nonspecific complaints such as headache, fatigue, lethargy, anorexia, vomiting, polydipsia, polyuria, and growth failure over a number of years.

The physical examination in patients with CKD can reveal pallor and a sallow appearance. Patients with long-standing untreated CKD can have short stature and the bony abnormalities of renal osteodystrophy (see Chapter 529.4). Children with CKD caused by chronic glomerulonephritis (or children with advanced renal failure from any cause) can have edema, hypertension, and other signs of extracellular fluid volume overload.

**LABORATORY FINDINGS**
Laboratory findings can include elevations in blood urea nitrogen and serum creatinine and can reveal hyperkalemia, hyponatremia (if volume overloaded), hypernatremia (loss of free water), acidosis, hypocalcemia, hyperphosphatemia, and an elevation in uric acid. Patients with heavy proteinuria can have hypoalbuminemia. A complete blood cell count may show a normochromic, normocytic anemia. Serum cholesterol and triglyceride levels are often elevated. In children with CKD caused by glomerulonephritis, the urinalysis shows hematuria and proteinuria. In children with CKD from congenital lesions

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**Table 535-7** | Pathophysiology of Chronic Kidney Disease
---|---
**MANIFESTATION** | **MECHANISMS**
Accumulation of nitrogenous waste products | Decrease in glomerular filtration rate
Acidosis | Decreased ammonia synthesis
| Impaired bicarbonate reabsorption
| Decreased net acid excretion
Sodium retention | Excessive renin production
| Oliguria
Sodium wasting | Solute diuresis
| Tubular damage
Urinary concentrating defect | Solute diuresis
| Tubular damage
Hyperkalemia | Decrease in glomerular filtration rate
| Metabolic acidosis
| Excessive potassium intake
| Hyporeninemic hypoaldosteronism
Renal osteodystrophy | Impaired renal production of 1,25-dihydroxycholecalciferol
| Hyperphosphatemia
| Hypocalcemia
| Secondary hyperparathyroidism
Growth retardation | Inadequate caloric intake
| Renal osteodystrophy
| Metabolic acidosis
| Anemia
| Growth hormone resistance
Anemia | Decreased erythropoietin production
| Iron deficiency
| Folate deficiency
| Vitamin B12 deficiency
| Decreased erythrocyte survival
Bleeding tendency | Defective platelet function
Infection | Defective granulocyte function
| Impaired cellular immune functions
| Indwelling dialysis catheters
Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy) | Uremic factor(s)
| Aluminum toxicity
| Hypertension
Gastrointestinal symptoms (feeding intolerance, abdominal pain) | Gastroesophageal reflux
| Decreased gastrointestinal motility
| Serositis (uremia)
Hypertension | Volume overload
| Excessive renin production
Hyperlipidemia | Decreased plasma lipoprotein lipase activity
Pericarditis, cardiomyopathy | Uremic factor(s)
| Hypertension
| Fluid overload
Glucose intolerance | Tissue insulin resistance
such as renal dysplasia, the urinalysis usually has a low specific gravity and minimal abnormalities by dipstick or microscopy. Inulin clearance is the gold standard to determine GFR, but it is not easy to measure. Endogenous creatinine clearance is the most widely used marker of GFR, but creatinine secretion falsely elevates the calculated GFR. Several other markers are under investigation to accurately determine GFR in children, such as cystatin C and iohexol. In children age 1-16 yr, the degree of renal dysfunction may be determined by applying a new bedside formula that estimates GFR between 15 and 75 mL/min/1.73 m²: estimated GFR = 0.43 × height in cm/ serum creatinine in mg/dL.

**TREATMENT**

The treatment of CKD is aimed at replacing absent or diminished renal functions, which progressively deteriorate in parallel with the progressive loss of GFR, and slowing the progression of renal dysfunction. Children with CKD should be treated at a pediatric center capable of supplying multidisciplinary services, including medical, nursing, social service, nutritional, and psychological support.

The management of CKD requires close monitoring of a patient's clinical and laboratory status. Blood studies to be followed routinely include serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, alkaline phosphatase, and hemoglobin levels. Periodic measurement of intact parathyroid hormone (PTH) levels and roentgenographic studies of bone may be of value in detecting early evidence of renal osteodystrophy. Echocardiography should be performed periodically to identify left ventricular hypertrophy and cardiac dysfunction that can occur as a consequence of the complications of CKD.

**Nutrition**

Nutritional management by a dietician experienced in pediatric renal patients is recommended by the National Kidney Foundation. Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Counseling based on individualized assessment should be considered for all children and their families with CKD stages 2 to 5 and 5D. Patients should receive 100% of estimated energy requirement for age, individually adjusted for physical activity level, body mass index, and response in rate of weight gain or loss. When oral supplemental nutrition with increased calories or fluid volume is insufficient, tube feeding should be considered. Calories should be balanced between carbohydrate, unsaturated fat in physiological ranges (per dietary reference intake [DRI]), and protein. Protein intake recommendation is 100-140% of the DRI for ideal weight for children with stage 3 CKD, 100-120% of the DRI in stages 4 and 5 CKD, and 100% with allowance for dialysis loss in CKD stage 5D, with use of commercial supplements as needed. Children with CKD stages 2-5 should receive 100% of DRI of vitamins and trace elements; water-soluble vitamin supplements are often required in CKD stage 5D.

**Renal Osteodystrophy**

The term renal osteodystrophy is used to indicate a spectrum of bone disorders seen in patients with CKD. The most common condition seen in children is high-turnover bone disease caused by secondary hyperparathyroidism. The skeletal pathologic finding in this condition is ostetitis fibrosa cystica.

The pathophysiology of renal osteodystrophy is complex. Early in the course of CKD, when the GFR declines to approximately 50% of normal, the decrease in functional kidney mass leads to a decline in renal 1α-hydroxylase activity, with decreased production of activated vitamin D (1,25-dihydroxycholecalciferol). This deficiency in activated vitamin D results in decreased intestinal calcium absorption, hypocalcemia, and increased parathyroid gland activity. Excessive PTH secretion attempts to correct the hypocalcemia by increasing bone resorption. Later in the course of CKD, when the GFR declines to 20-25% of normal, compensatory mechanisms that have been operative to enhance renal phosphate excretion become inadequate, resulting in hyperphosphatemia, which further promotes hypocalcemia and increased PTH secretion.

Clinical manifestations of renal osteodystrophy include muscle weakness, bone pain, and fractures with minor trauma. In growing children, rachitic changes, varus and valgus deformities of the long bones, and slipped capital femoral epiphyses may be seen. Laboratory studies can demonstrate a decreased serum calcium level and increased serum phosphorus, alkaline phosphatase, and PTH levels. Radiographs of the hands, wrists, and knees show subperiostal resorption of bone with widening of the metaphyses.

The goals of treatment are to prevent bone deformity and normalize growth velocity using both dietary and pharmacologic interventions. The target phosphorus level for adolescents is between 3.5 and 5.5 mg/dL, and for children 1-12 yr of age it is 4-6 mg/dL. Children and adolescents should follow a low-phosphorus diet, and infants should be provided with a low-phosphorus formula such as Similac PM 60/40. It is impossible to fully restrict phosphorus intake, and so phosphate binders are used to enhance GI phosphate excretion. Although calcium-based binders have historically been the most commonly used, non–calcium-based binders such as sevelamer (Renagel) are increasing in use, particularly in older children and adolescent patients who are prone to hypercalcemia. Because aluminum may be absorbed from the GI tract and can lead to aluminum toxicity, aluminum-based binders should be avoided.

The cornerstone of therapy for renal osteodystrophy is vitamin D administration. Vitamin D therapy is indicated in patients with 1,25-dihydroxy-vitamin D levels below the established goal range for the child's particular stage of CKD or in patients with PTH levels above the established goal range for CKD stage. Patients with low 1,25-dihydroxy-vitamin D and elevated PTH levels should be treated with 0.01-0.05 µg/kg/24 hr of calcitriol (Rocaltrol, 0.25-µg capsules or 1 µg/mL suspension). Newer activated vitamin D analogs such as paricalcitol and doxercalciferol are increasingly used, especially in patients who are predisposed to hypercalcemia. Phosphate binders and vitamin D should be adjusted to maintain the PTH level within the designated goal range and the serum calcium and phosphorus levels within the normal range for age. Many nephrologists also attempt to maintain the calcium/phosphorus product (Ca × P) at <55 mg²/dL² in adolescents and <65 mg²/dL² in younger children to minimize the possibility of tissue deposition of calcium phosphorus salts with consequent damage.

**Adynamic Bone Disease**

Adynamic bone disease (low-turnover bone disease) has been recognized in children and adults with CKD. The pathologic finding is osteomalacia and is associated with oversupply of PTH, perhaps related to the widespread use of calcium-containing phosphate binders and vitamin D analogs.

**Fluid and Electrolyte Management**

Most children with CKD maintain normal sodium and water balance, with the sodium intake derived from an appropriate diet. Infants and children whose CKD is a consequence of renal dysplasia may be polyuric, with significant urinary sodium or free water losses. These children may benefit from high-volume, low-caloric-density feedings with sodium supplementation. Children with high blood pressure, edema, or heart failure may require sodium restriction and diuretic therapy. Fluid restriction is rarely necessary in children with CKD until the development of ESRD requires the initiation of dialysis.

In most children with CKD, potassium balance is maintained until renal function deteriorates to the level at which dialysis is initiated. Hyperkalemia can develop, however, in patients with moderate renal insufficiency who have excessive dietary potassium intake, severe acidosis, or hyporeninemic hypoaldosteronism (related to destruction of the renin-secreting juxtaglomerular apparatus). Hyperkalemia may be treated by restriction of dietary potassium intake, administration of oral alkalinizing agents, and/or treatment with Kayexalate.

**Acidosis**

Metabolic acidosis develops in almost all children with CKD as a result of decreased net acid excretion by the failing kidneys. Either Bicita
According to the schedule used for healthy children. An exception must be made in withholding live virus vaccines from children with CKD related to glomerulonephritis, or any disease, during treatment with immunosuppressive medications. It is critical, however, to make every attempt to administer live virus vaccines for measles, mumps, rubella, and varicella before kidney transplantation. These vaccines are not advised for use in immunosuppressed patients. All children with CKD should receive a yearly influenza vaccine. Data from a number of studies suggest that children with CKD might respond suboptimally to immunizations.

Adjustment In Drug Dose

Because many drugs are excreted by the kidneys, their dosing might need to be adjusted in patients with CKD to maximize effectiveness and minimize the risk of toxicity. Strategies in dosage adjustment include lengthening of the interval between doses or decreasing the absolute dose, or both. Such adjustments become even more important as pharmacogenomic profiling of drug metabolism becomes routine.

Progression of Disease

Although there are no definitive treatments to improve renal function in children or adults with CKD other than treatment of a specific underlying disorder when possible, there are several general strategies that may be effective in slowing the rate of progression of renal dysfunction. Optimal control of hypertension (maintaining the blood pressure at lower than the 75th percentile and perhaps even lower) is critical in all patients with CKD. ACE inhibitors or angiotensin II receptor blockers should be the antihypertensive drugs of choice in hypertensive children with chronic proteinuric renal disease as previously noted. Such agents should also be strongly considered in children with CKD who have significant proteinuria, even in the absence of hypertension, although there are no controlled studies to support this approach. Serum phosphorus should be maintained within the normal range for age and the calcium–phosphorus product <55 to minimize renal calcium–phosphorus deposition. Prompt treatment of infectious complications and episodes of dehydration can minimize additional loss of renal parenchyma.

Other potentially beneficial recommendations include correction of anemia with erythropoietin or darbepoetin alfa therapy, control of hyperlipidemia, avoidance of cigarette smoking, prevention of obesity, and avoidance of nonsteroidal antiinflammatory and other potential nephrotoxic medications. This includes a variety of illegal street drugs as well as herbal and/or homeopathic medications or “supplements.” Although dietary protein restriction may be useful in adults, this recommendation is generally not suggested for children with CKD because of the concern about adverse effects on growth and development.

Bibliography is available at Expert Consult.

535.3 End-Stage Renal Disease

Rajasree Sreedharan and Ellis D. Avner

ESRD represents the state in which a patient's renal dysfunction has progressed to the point at which homeostasis and survival can no longer be sustained with native kidney function and maximal medical management. At this point, renal replacement therapy (dialysis or renal transplantation) becomes necessary. The ultimate goal for children with ESRD is successful kidney transplantation (see Chapter 536).
Bibliography


because it provides the most normal lifestyle and possibility for rehabilitation for the child and family.

In the United States, 75% of children with ESRD require a period of dialysis before transplantation can be performed. It is recommended that plans for renal replacement therapy be initiated when a child reaches stage 4 CKD. The optimal time to actually initiate dialysis, however, is based on a combination of the biochemical and clinical characteristics of the patient including refractory fluid overload, electrolyte imbalance, acidosis, growth failure, or uremic symptoms, including fatigue, nausea, and impaired school performance. In general, most nephrologists attempt to initiate dialysis early enough to prevent the development of severe fluid and electrolyte abnormalities, malnutrition, and uremic symptoms. Preemptive transplantation before initiation of dialysis is increasingly being utilized.

The selection of dialysis modality must be individualized to fit the needs of each child. In the United States, two thirds of children with ESRD are treated with peritoneal dialysis, whereas one third are treated with hemodialysis. Age is a defining factor in dialysis modality selection: 88% of infants and children from birth to 5 yr of age are treated with peritoneal dialysis, and 54% of children >12 yr of age are treated with hemodialysis.

**Peritoneal dialysis** is a technique that employs the patient’s peritoneal membrane as a dialyzer. Excess body water is removed by an osmotic gradient created by the high dextrose concentration in the dialysate; wastes are removed by diffusion from the peritoneal capillaries into the dialysate. Access to the peritoneal cavity is achieved by a surgically inserted, tunneled catheter.

Peritoneal dialysis may be provided either as continuous ambulatory peritoneal dialysis or as an automated therapy using a cycler (continuous cyclic peritoneal dialysis, intermittent peritoneal dialysis, or nocturnal intermittent peritoneal dialysis). The majority of U.S. children treated with peritoneal dialysis use cycler-driven therapy, which allows the child and family to be free of dialysis demands during the waking hours. The exchanges are performed automatically during sleep by machine. This permits an uninterrupted day of activities, a reduction in the number of dialysis catheter connections and disconnections (which decreases the risk of peritonitis), and a reduction in the time required by patients and parents to perform dialysis, reducing the risk of fatigue and burnout. Because peritoneal dialysis is not as efficient as hemodialysis, it must be performed daily rather than 3 times weekly. Table 535-8 outlines the benefits of peritoneal dialysis.

**Hemodialysis**, unlike peritoneal dialysis, is usually performed in a hospital setting. Children and adolescents typically have 3 treatments (3-4 hr each) per wk during which fluid and solute wastes are removed. Access to the child's circulation is achieved by a surgically created arteriovenous fistula, graft, or indwelling subclavian or internal jugular catheter.

*Bibliography is available at Expert Consult.*

<table>
<thead>
<tr>
<th>Table 535-8</th>
<th>Merits of Peritoneal Dialysis in Pediatric Patients with End-Stage Renal Disease</th>
</tr>
</thead>
</table>
| **ADVANTAGES** | Ability to perform dialysis treatment at home  
Technically easier than hemodialysis, especially in infants  
Ability to live a greater distance from medical center  
Freedom to attend school and after-school activities  
Less-restrictive diet  
Less expensive than hemodialysis  
Independence (adolescents) |
| **DISADVANTAGES** | Catheter malfunction  
Catheter-related infections (peritonitis, exit site)  
Impaired appetite (due to full peritoneal cavity)  
Negative body image  
Caregiver burnout |
Bibliography


Kidney transplantation is the optimal therapy for children with end-stage renal disease (ESRD). Five yr survival rates in children who receive a kidney transplant are greater than survival rates of those who remain on hemodialysis or peritoneal dialysis. Children and adolescents with ESRD have special needs that differ from adults, including the need to achieve normal growth and cognitive development. Successful transplantation leads to improvement in their linear growth and allows them to attend school and be free of dietary restrictions. Immunosuppression protocols that employ steroid minimization or avoidance after transplantation demonstrate dramatic improvements in growth patterns for young children after transplantation. Improvements in surgical techniques and a reduction in the early complications of thrombosis have given young children the best long-term outcomes of all age groups among transplant recipients.

**INCIDENCE AND ETIOLOGY**
The incidence of ESRD in pediatric patients in the United States varies by age group (Table 536-1). There is an adjusted incident rate of 14.4 per million population for ages 0-19 yr.

The etiology of ESRD in children varies significantly by age (Table 536-2). Congenital, hereditary, and cystic diseases cause ESRD in more than 52% of children 0-4 yr of age, whereas glomerulonephritis and focal segmental glomerulosclerosis (FSGS) account for 38% of cases of ESRD in patients 10-19 yr of age. The most common diagnosis in children with transplanted kidneys is structural disease (49%), followed by various forms of glomerulonephritis (14%) and FSGS (12%).

**INDICATIONS**
Almost all children with ESRD are considered to be candidates for renal transplantation. There are very few absolute contraindications for pediatric kidney transplantation. Relative contraindications include children with preexisting metastatic malignancy or HIV. Patients with remission of malignancy off maintenance treatment for a minimum of 2 yr may be reconsidered on an individual basis for transplantation, with close posttransplantation surveillance. Similarly, patients with autoimmune diseases resulting in ESRD are candidates for transplantation after a period of immunologic quiescence of the primary disease for a period of at least 1 yr before transplantation. Another relative contraindication includes severe neurologic dysfunction, but the wishes of the parents and the potential for rehabilitation must be considered.

<table>
<thead>
<tr>
<th>Table 536-1</th>
<th>Incident Rates of Reported ESRD in the United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE RANGE (YR)</td>
<td>ADJUSTED INCIDENT RATES* PER MILLION POPULATION</td>
</tr>
<tr>
<td>0-4</td>
<td>9.5</td>
</tr>
<tr>
<td>5-9</td>
<td>6.1</td>
</tr>
<tr>
<td>10-14</td>
<td>13</td>
</tr>
<tr>
<td>15-19</td>
<td>29</td>
</tr>
</tbody>
</table>

*Rates are adjusted for sex and race.
ESRD, end-stage renal disease.

Table 536-2 Common Causes of ESRD in Pediatric Transplant Recipients (N = 9854)

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>% OF RECIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplasia, hypoplasia, dysplasia</td>
<td>15.9</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>15.6</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>11.7</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>5.2</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>3.3</td>
</tr>
<tr>
<td>Polycystic disease</td>
<td>2.9</td>
</tr>
<tr>
<td>Medullary cystic disease</td>
<td>2.8</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
<td>2.6</td>
</tr>
<tr>
<td>Prune belly syndrome</td>
<td>2.6</td>
</tr>
<tr>
<td>Congenital nephrotic syndrome</td>
<td>2.6</td>
</tr>
<tr>
<td>Familial nephritis</td>
<td>2.3</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>2.0</td>
</tr>
<tr>
<td>Idiopathic crescentic glomerulonephritis</td>
<td>1.7</td>
</tr>
<tr>
<td>MPGN type I</td>
<td>1.7</td>
</tr>
<tr>
<td>Berger (IgA) nephritis</td>
<td>1.3</td>
</tr>
<tr>
<td>Henoch-Schönlein nephritis</td>
<td>1.1</td>
</tr>
<tr>
<td>MPGN type II</td>
<td>0.8</td>
</tr>
</tbody>
</table>

ESRD, end-stage renal disease; MPGN, membranoproliferative glomerulonephritis.

Data from the North American Pediatric Renal Trials and Collaborative Studies, https://web.emmes.com/study/pedt/.

Renal transplantation is considered for any child when renal replacement therapy is indicated. In children, dialysis may be required for a period before transplantation to optimize nutritional and metabolic conditions, to achieve an appropriate size in small children, or to keep a patient stable until a suitable donor is available. For young infants, a recipient may need to weigh at least 8-10 kg to minimize the risk for vascular thrombosis and to accommodate a adult-size kidney. This can require a period of dialysis support until the child is at least 12-18 mo of age. Transplantation with an adult-size kidney has been successful in children who weighed <10 kg or were <6 mo of age.

Preemptive transplantation (i.e., transplantation without prior dialysis) continues to account for approximately 25% of all pediatric renal transplants, based mostly on a desire by the child and the family to avoid dialysis. There may be a small benefit in allograft outcome if transplantation occurs without prior dialysis, which might relate to a lower incidence of infections and cardiovascular risk factors. Preemptive renal transplant should be considered when the glomerular filtration rate (GFR) is <10-15 mL/min/1.73 m² and with symptomatic ESRD or rapidly declining GFR and need for dialysis within 6-12 mo. The rates of preemptive transplantation differ moderately for different age groups, being 20% for recipients age ≤2 yr, 24% for age 2-5 yr, 28% for age 6-12 yr, and 22% for age 13-17 yr.

CHARACTERISTICS OF DONORS AND RECIPIENTS

Almost half of all pediatric kidney transplants come from living donors. The highest rates of transplantation are in the 5-9 yr old group, with 40 live donor transplants and 46 cadaver donor transplants performed per 100 dialysis patient-years. The Organ Procurement and Transplantation Network (OPTN) provides preference for children waiting for a deceased-donor renal transplant. Owing to improved outcomes in deceased-donor pediatric transplantation using donors 5-35 yr of age, OPTN in 2005 implemented a pediatric kidney allocation policy that gave priority for kidneys from deceased donors <35 yr of age. These kidneys were assigned to recipients <18 yr, after 0 mismatch transplants, recipients with a panel reactive antibody >80, or candidates receiving a kidney with a nonrenal origin. This policy shortened the wait time for children versus adults and is associated with improved outcomes.

Living-donor kidney transplantation graft survival has improved over the years, and from 2003-2007 the graft survival rate in living-donor renal transplants was 96.1%, unchanged from the 1999-2002 rate of 95.9%. Graft survival rates for deceased donors from 2003-2007 are 94.4%, also improved from 92.7% in 1999-2002. For children awaiting deceased-donor renal transplants the goals are to minimize waiting times, transplanting kidneys into children 0-6 yr of age within 6 mo, children 7-12 yr within 12 mo, and children 12-18 yr within 18 mo.

EVALUATION AND PREPARING FOR TRANSPLANTATION

The team approach includes evaluations by a transplantation surgeon, nephrologist, nutritionist, social worker, psychologist, financial counselor, pretransplantation nurse, and dialysis nurse (if the patient is undergoing dialysis).

Primary renal disease can recur in a number of renal diseases, but it is not a contraindication to transplantation. Recurrent disease in the renal graft accounts for graft loss in almost 7% of primary transplants and 10% in repeat transplantsations.

With FSGS and primary oxalosis, patients are at risk for major renal function impairment with recurrence of disease. Grafts in approximately 20-30% of patients with the diagnosis of FSGS fail because the disease recurs. In patients with the original disease of FSGS whose grafts fail, the mean time to failure is 17 mo. Alport syndrome can recur as an anti–glomerular basement membrane (anti–GBM) glomerulonephritis in approximately 3-4% of patients after transplantation and lead to graft loss. Histologic evidence of recurrence of membranoproliferative glomerulonephritis type II occurs in virtually all cases, with graft loss in ≤50% cases. Histologic recurrence of membranoproliferative glomerulonephritis type II disease occurs in virtually all cases, with graft loss in ≤50% cases. Histologic recurrence with mesangial immunoglobulin (Ig) A deposits is common and occurs in about half of the patients with IgA nephropathy and in approximately 30% of patients with Henoch-Schönlein purpura. Congenital nephrotic syndrome rarely recurs after transplantation, although patients can develop antinephrin antibodies and present with nephrotic syndrome. Some cases (~25%) of nephrotic syndrome after transplantation are likely de novo. Membranous nephropathy occurs very rarely in children. The recurrence rate after kidney transplantation for patients who have been treated for Wilms tumor is approximately 13%.

Owing to the high risk of developing Wilms tumor, patients with Denys-Drash syndrome should undergo bilateral nephrectomy before transplantation. Other indications for bilateral native nephrectomies include hypoplasia with polyuria, significant proteinuria, and severe hypertension resistant to medical management. Nephrectomies are also indicated in cases such as polycystic kidney disease, where more room may be needed to place the transplanted kidney and to create space in the abdominal cavity to improve feeding tolerability and the infant’s ability to thrive.

Failure to maintain adequate perfusion of the adult-size kidney, secondary to a “perfusion steal” by the native kidneys results in a histologic picture of “chronic” acute tubular necrosis and a negative impact on graft function.

Urologic problems, such as vesicoureteral reflux, posterior urethral valves, abnormal urinary bladders, and/or neurogenic bladders, should be addressed before surgery. Malformations and voiding abnormalities (e.g., neurogenic bladder; bladder dyssynergia, remnant posterior urethral valves, and urethral strictures) should be identified and repaired if possible. Children with urologic disease and renal dysplasia often require multiple operations to optimize urinary tract anatomy and function. Such procedures include ureteric reimplantation to correct vesicoureteral reflux, bladder augmentation or reconstruction, creation of a vesicocutaneous fistula by using the appendix to provide a simple, continent, and cosmetically acceptable way for intermittent
catheterization (Mitrofanoff procedure), and excision of duplicated systems or ectopic ureteroceles that could cause recurrent infections. There are reports of excellent outcomes often being achieved in posterior urethral valve bladders by following a staged procedure of initial valve resection to limit any injury to the posterior urethra, and bladder rehabilitation, without the requirement of augmentation, by a process of regimented double voiding.

A comprehensive nutritional assessment needs to be done to ensure that optimal nutritional status is achieved before transplant. Many children with ESRD and especially those on dialysis require nutritional supplements to provide them with sufficient protein and calories. Infants and young children on dialysis often require nasogastric or gastric tube feedings to overcome decreased oral intake from nausea and anorexia due to uremia. Optimal outcomes result from transplanting adult-size kidneys from living donors when the child weighs ≥10 kg.

Bone disease needs to be evaluated for and treated before transplantation. Secondary hyperparathyroidism needs to be treated before transplant to avoid posttransplant urinary phosphate wasting and hypercalcemia. High calcium phosphorus product before transplantation leads to vascular stiffness and calcifications, increasing the patient’s risk for cardiovascular disease.

In the United States, >25% of the mortality in children on maintenance dialysis is a result of cardiovascular disease. Cardiac death is the leading cause of death in young patients after transplant in childhood. Therefore, evaluation of cardiac function is required before a kidney transplant in a pediatric patient to be sure that patient has sufficient cardiac function to tolerate the large fluid load that accompanies kidney transplantation. All patients being evaluated for kidney transplant have at least an echocardiogram and electrocardiogram. Hypertension is common and can result from fluid overload and/or intrinsic native renal disease. Blood pressure needs to be under optimal control before transplant. If blood pressure cannot be controlled with medical management, bilateral nephrectomy may need to be performed before transplant to control the hyperreninemic response from the failing kidneys.

Anemia needs to be treated before transplantation. Most patients are taking erythropoietin, folate, and iron to maintain goals for hemoglobin levels between 11 and 12 g/dL. Blood transfusions should be avoided owing to concerns for sensitizing the patient to human leukocyte antigens before transplant. If a blood transfusion is required, patients should receive cytomegalovirus negative, leukoreduced red blood cells. Blood should not be irradiated owing to concerns for trauma to the cells and potential for increased antigen exposure.

Evaluation for venous thrombosis and hypercoagulable states is important before renal transplantation. The third leading cause of graft failure is vascular thrombosis; the leading causes are chronic (34.9%) and acute (13.1%) rejection. Risk factors for graft thrombosis include surgical technique, perfusion and reperfusion injury of graft, young donor age (<2 yr), young recipient (<5 yr), cold ischemia time >24 hr, arterial hypotension, prior history of peritoneal dialysis, and/or hypo-perfusion of adult kidney transplant in a small child. Particularly in the young recipient, before transplantation, there needs to be evaluation for thrombosis of iliac vessels or inferior vena cava if the patient has had previous surgery or central line placement. Femoral line catheterizations greatly increase the risk for inferior vena cava thrombosis. Children who have large protein losses, such as from nephrotic syndrome and/or peritoneal dialysis, can be at increased risk for thrombosis because of protein loss, such as protein S, protein C, and antithrombin III. Doppler ultrasound, computed tomographic angiography, and magnetic resonance angiography have all been used to evaluate vessels. Magnetic resonance angiography has been used less owing to the concern about exposure to gadolinium and nephrogenic systemic fibrosis. In patients with renal compromise receiving contrast media, intravenous hydration is needed before and after the study for patients with residual renal function, acidosis should be corrected before giving contrast, and N-acetyl cysteine should be administered before and after the CT angiogram to reduce the risk of contrast nephropathy. If the patient is on dialysis, dialysis clearance can be done after contrast administration; hemodialysis is the optimal method for clearance.

Infections need to be identified and treated before transplantation. Infectious disease screening includes a complete history of household contacts with treatment for active or latent tuberculosis, vaccine history for varicella and pertussis, travel history within the past 2 yr and/or if there was significant time spent in another country, history of bacille Calmette-Guérin, animal and/or insect exposure, sexual activity, and consumption of high-risk foods such as unpasteurized products. Screening includes tuberculosis skin test (purified protein derivative), cytomegalovirus IgG, Epstein-Barr virus (EBV) antibody panel, varicella titer, measles antibody, hepatitis B serologies, hepatitis C antibody, HIV, and toxoplasmosis. Additional testing for patients who lived in or visited the central valleys of California, Utah, Nevada, Arizona, and/or New Mexico includes Coccidioides immunodiffusion. Patients from the Ohio River valley should also have Histoplasma antibody checked. Patients from Mexico should have Coccidioides immunodiffusion, Histoplasma antibody, and ova and parasite screen to evaluate for Strongyloides. Those from South America should have Coccidioides immunodiffusion, Histoplasma antibody, and Toxoplasma antibody. Sexually active patients should also be screened for syphils, gonorrhea, HIV, and Chlamydia.

Immunizations need to be up to date before transplantation. All live vaccines need to be given before transplantation because these vaccines should not be given to immunosuppressed patients. Therefore, measles-mumps-rubella and varicella should be given before transplant and antibody titers should be checked to monitor for response. Measles-mumps-rubella may be given as early as 6 mo of age. Inhaled influenza vaccine should not be given to transplant patients, family members, or healthcare providers.

Psychiatric evaluation should be performed before transplantation to evaluate patients’ and their families’ ability to cope with the stresses that accompany caring for a child with a kidney transplant. A psychologist should also evaluate the patient and their caregivers for depression, substance abuse, and/or noncompliance so that problems can be identified and managed before kidney transplantation. If non-compliance is identified or anticipated, interventions should be in place before transplantation. These should include social and psychiatric interventions, where possible.

Children need 2 ABO blood types checked before being listed for a kidney transplantation and a donor should be sought who shares HLA-A, HLA-B, and/or HLA-DR antigens. The 2008 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) data have shown increased risk for rejection and graft failure with 2-DR mismatch compared to a 0-DR mismatch. The recipient’s blood is also checked to see if the patient is sensitized. Patients can become sensitized by prior transplant, blood transfusions, sepsis, and/or pregnancy.

**IMMUNOSUPPRESSION**

Most pediatric kidney transplant centers employ a combination of drug therapy consisting of a calcineurin inhibitor and corticosteroids with or without an antiproliferative agent. Approximately 80% of transplantation patients receive a 3-drug regimen at 6 mo after transplantation. The rationale for this combination therapy in children is to provide effective immunosuppression and at the same time minimize the toxicity of any single drug.

**Induction Therapy**

Induction therapy is commonly used in pediatric renal transplant recipients to prevent acute rejection. Graft survival rates are higher in patients treated with antithymocyte induction therapy. Acute rejection episodes are approximately 30% less frequent and tend to occur later. Induction therapy may consist of T-cell antibodies, interleukin-2 receptor antibodies, and/or therapies that target B cells.

**T-Cell Antibodies**

Antithymocyte globulin (ATGAM) and Thymoglobulin are polyclonal antibodies that should be given intravenously through a central line to avoid sclerosis and injury to smaller vessels. These medications are
used to prevent the development of the first rejection. Thymoglobulin is polyclonal antibodies against human T-lymphocyte antigens resulting in a rapid depletion of T lymphocytes. Some limit the use of Thymoglobulin induction to sensitized high-risk patients or patients who have concerns for delayed graft function and want to avoid high calcineurin inhibitor levels in the early postoperative period. Dosage is 1.5-2.0 mg/kg/dose, with daily monitoring of CD3+ subsets; the dose should not be given if the CD3+ count exceeds 20 cells/mm³.

OKT3 is a monoclonal antibody that is also given daily for 10-14 days. Studies have not shown a clear advantage using OKT3.

Interleukin-2 Receptor Antibodies
Monoclonal antibodies, such as basiliximab and daclizumab, chimeric or humanized monoclonal anti-CD25 antibodies, prevent T-cell proliferation but do not cause T-cell depletion. Basiliximab is given on day 0 and day 4 of the transplant as 12 mg/m²/dose in children. Daclizumab is given on day 0 and then every 2 wk for a total of 5 doses at 1 mg/kg/dose in patients with steroid-based immunosuppression. Patients who are steroid free receive a 2 mg/kg/dose on day 0 and the remaining doses at 1 mg/kg at wk 2, 4, 6, 8, 11, 15, 19, and 23. This provides the patient with extra immunosuppression for 3 mo for steroid-based patients and 6 mo for steroid-free patients. Patients tend to tolerate IL-2 receptor antagonists well. With the withdrawal of daclizumab from the market because of manufacturing defects, many pediatric transplantation programs are using basiliximab or a short course (3 days) of Thymoglobulin at 1.5 mg/kg/day for children at low risk of sensitization and the recommended dosing of Thymoglobulin (5-7 days) or alemtuzumab for children at high risk of sensitization (see below).

Alemtuzumab (Campath-1H) is a monoclonal antibody against CD52 antigen present on T and B cells, monocytes, and natural killer cells. The pediatric data on the use of alemtuzumab show promising results.

Other Induction Therapies
Other induction therapies for highly sensitized patients include targeting B cells and/or removing neutralizing antibodies by using rituximab against the CD20 epitope on early- and intermediate-lineage B cells, the proteosome inhibitor bortezomib, and plasmapheresis and/or high-dose intravenous immunoglobulin for removing donor-specific antibodies.

Belatacept is a fusion protein composed of the Fc fragment of a human IgG, linked to the extracellular domain of CTLA-4, which is a molecule crucial for T-cell costimulation, selectively blocking the process of T-cell activation. Belatacept usage extends from induction to limited maintenance therapy, and is intended to provide optimal immunosuppression and limiting of the toxicity generated by standard immune-suppressing regimens, such as calcineurin inhibitors, thus limiting fibrosing graft injury and improving renal function. Complications include a higher incidence and grade of acute rejection episodes and a higher incidence of posttransplant lymphoproliferative disorders, with greatest risk in EBV seronegative recipients.

Maintenance Immunosuppression
For maintenance immunosuppression, calcineurin inhibitors, mycophenolate mofetil (MMF), steroids, azathioprine, and/or rapamycin may be used. Most pediatric kidney transplant recipients are maintained with a triple-immunosuppressant regimen. Central to many current pediatric immunosuppressive regimens is a calcineurin inhibitor (cyclosporine or tacrolimus) in combination with steroids and an adjunctive antiproliferative agent (azathioprine, sirolimus, or MMF). MMF is used as the adjunctive agent in more than two thirds of the pediatric kidney transplants performed. Sirolimus is used in 10-15%, and azathioprine is used in only approximately 2%. Corticosteroids continue to be used in approximately 80-85% of transplant recipients.

Calcineurin Inhibitors
The side-effect profile of cyclosporine in children is similar to that seen in adults, but the impact on children is more pronounced. Hypertrichosis, gingival hyperplasia, and coarsening facial features may be particularly troublesome in children. Hispanic and African-American children appear to be at higher risk for significant hypertrichosis. In the adolescent population, especially girls, these side effects can cause severe emotional distress, possibly leading to noncompliance. Seizures, although uncommon, are observed more commonly in children treated with cyclosporine than in adults. Children are likely to develop hypercholesterolemia and hypertriglyceridemia and may be candidates for lipid-lowering agents. Hyperglycemia occurs in <5% of children treated with cyclosporine.

The hyperlipidemia associated with cyclosporine and other immunosuppressive agents is also absent with tacrolimus. On the other hand, posttransplantation glucose intolerance, tremor, alopecia, and mild sleep disturbances are more common with tacrolimus. Historically, posttransplant lymphoproliferative disease has been significantly more common in children receiving tacrolimus. The lack of cosmetic side effects makes tacrolimus a very attractive alternative for children. This is especially true for young adolescents and female patients, in whom the cosmetic side effects can lead to noncompliance.

Direct comparative data in pediatrics between cyclosporine and tacrolimus are limited. The published results comparing these 2 agents show that overall acute rejection rates at 6 mo were 59.1% versus 36.9% for cyclosporine and tacrolimus, respectively. In the tacrolimus group, graft function was better at 1 yr after transplantation. The mean total steroid dose from time of transplant to 6 mo posttransplantation was significantly lower in the tacrolimus group. The overall safety profiles of the 2 calcineurin inhibitors were equivalent, with essentially no difference in posttransplant lymphoproliferative disorder or in diabetes requiring insulin treatment. The combination of drugs (tacrolimus and sirolimus) may be the biggest risk factor for PTLD.

Mycophenolate Mofetil
MMF is the morpholinooethyl ester drug of mycophenolic acid, an inhibitor of de novo purine synthesis. MMF is part of the initial maintenance immunosuppression regimen in approximately 66% of U.S. pediatric renal transplant recipients. It has largely replaced azathioprine. Acute rejection rates with MMF are approximately 20-30% when used with cyclosporine and corticosteroids. When MMF is used with tacrolimus and/or humanized monoclonal antibodies to the IL-2 receptor, lower rejection rates are usually seen.

The use of MMF has often facilitated the use of a lower dose of corticosteroids after transplantation. It has also proved useful in calcineurin inhibitor-sparing protocols, in which MMF is combined with sirolimus and corticosteroids. In steroid-avoidance regimens in kidney transplantation, the bioavailability of mycophenolic acid has been found to be greater than when the drug is used with steroids. This has allowed reduced dosing of MMF when combined with steroid avoidance in children. The absence of nephrotoxicity, hyperlipidemia, and hepatotoxicity has also contributed to the usefulness of MMF.

Gastrointestinal and hematologic side effects can be troublesome. Most of these instances can be treated with a dosage reduction and/or brief discontinuation of the drug, with resumption after 7-14 days at a lower dose. Enteric-coated mycophenolic acid has been shown to decrease the upper gastrointestinal side effects of MMF in adult transplant recipients.

Sirolimus
Sirolimus, an inhibitor of the mammalian target of rapamycin, used primarily as an adjunctive immunosuppressive agent in combination with a calcineurin inhibitor. It is used in approximately 10-15% of pediatric renal transplant recipients. Limited anecdotal experience with sirolimus as a rescue agent in cases of refractory acute rejection, chronic allograft nephropathy, calcineurin inhibitor nephrotoxicity, and PTLD has been promising.

Most early reports in pediatric kidney transplantation appear to describe combinations of sirolimus with either tacrolimus or MMF; usually these are combined with prednisone, although efficacy has also been demonstrated with dual therapy (MMF and sirolimus) with complete steroid avoidance.
Corticosteroids
Corticosteroids remain an integral part of many immunosuppressive protocols despite their multifaceted toxicities. In children, retarded skeletal growth is the most noteworthy side effect of corticosteroids. Concerns remain about side effects, such as hypertension, obesity, diabetes mellitus, hyperlipidemia, osteopenia, and aseptic necrosis of bone (particularly the femoral heads). Cosmetic side effects, such as cushingoid faces and acne, are significant additional problems of chronic steroid use. Such side effects often tempt children and adolescent to stop taking their immunosuppressive drugs.

Steroid withdrawal attempts have led to improvements in blood pressure, lipid profiles, and growth. The benefits of steroid withdrawal have been overshadowed by high rates of acute rejection that occur in 25-70% of children. Studies using tacrolimus maintenance have shown safety in late steroid withdrawal, with low rates of acute rejection and no rebound early rejections. A steroid withdrawal trial using sirolimus had low rates of acute rejection but a high incidence of PTLD, which resulted in premature discontinuation of the study.

Complete steroid avoidance has emerged as an alternative strategy to prevent steroid-associated morbidities in children. The immunologic outcomes of these studies are the lower rates of acute rejection seen in these studies compared with standard of care protocols using steroids, suggesting that steroid avoidance might also have immunologic benefits. Building on such observations, investigators at a single center (Stanford University, Stanford, CA) initiated a steroid-avoidance protocol and demonstrated that complete steroid avoidance can be successfully achieved with excellent long-term outcomes at 8 yr, using tacrolimus in combination with MMF, and an extended 6 mo course of daclizumab. Other centers have had similar experience with complete steroid avoidance, using a similar protocol with tacrolimus and MMF and induction with either extended daclizumab or Thymoglobulin. The Stanford steroid-avoidance protocol has been replicated in a randomized multicenter U.S. trial (NIH/NIAID/CCPTP U01 AI-55795) across 12 different pediatric kidney transplant programs in the United States, and this seminal trial confirms the safety of steroid avoidance in low-risk pediatric kidney transplant recipients with lower acute rejection rates, and significant benefits for growth, hypertension, and hyperlipidemia. Importantly, this study also confirmed the overall safety of steroid avoidance, with no adverse effects on generation of donor-specific antibody posttransplantation or histologic injury.

Fluid Management in Infants and Small Children
Maintenance of adequate blood flow to an adult-sized kidney in an infant or small child is crucial to avoid acute tubular necrosis (ATN) and graft loss from vascular thrombosis and primary nonfunction. The recipient aortic blood flow early after transplantation of an adult-size kidney more than doubles from pretransplantation aortic blood flow. The maximum blood flow that can be obtained in an adult-size kidney transplanted into a small child is approximately 65% of what was in the donor. Low blood flow states such as with hypovolemia or hypotension increase the risk for ATN, graft thrombosis, and graft nonfunction. In the postoperative period, patients are maintained on high fluid volumes.

Close attention is paid to blood pressure and hydration status in the operating room in an attempt to reduce the incidence of delayed graft function. Typically, a central venous catheter is inserted to monitor the central venous pressure throughout the operation. To achieve adequate renal perfusion, a central venous pressure of 12-15 cm H2O should be achieved before removing the vascular clamps; a higher central venous pressure may be desirable in the case of a small infant receiving an adult-size kidney. Dopamine is usually started in the operating room at 2 to 3 µg/kg/min, increased if required, and continued for 24-48 hr postoperatively. It is used to facilitate diuresis and perhaps to affect renal vasodilation. The mean arterial blood pressure is kept >65-70 mm Hg by adequate hydration with a crystalloid solution and 5% albumin, and, if necessary, by using dopamine at higher doses. A blood transfusion with packed red blood cells may be required in very small recipients because the hemoglobin can drop as a result of sequestration of approximately 150-250 mL of blood in the transplanted kidney. Mannitol and/or furosemide may be given before removing the vascular clamps to increase the effective circulatory volume and facilitate diuresis. Mannitol can also act as a free-radical scavenger, and together with renal dose dopamine it is a critical factor for minimizing the ischemia–reperfusion injury in steroid-avoidance regimens. After the transplanted kidney starts to produce urine, volume replacement should be immediately started with normal saline.

Infants continue to receive aggressive fluid management by nasogastric or gastrostomy tube feedings of at least 2500 mL/m2/day for 26 mo after transplant if the child is unable to take in sufficient volume. This aggressive fluid management showed 30 mL/min greater GFR in infants who received adult-size kidneys and who were maintained on this higher fluid requirement than infants who were not.

Renal Biopsy
Renal biopsy is the gold standard for diagnosis of acute allograft dysfunction. Protocol biopsies may improve graft outcome by detecting early pathology and help monitor drug nephrotoxicity. The largest serial analysis of protocol biopsies at implantation, 3, 6, 12, and 24 mo posttransplantation (the NIH SNSO1 trial, 2004-9) established that the prime risk factor for chronic histologic injury was discrepancy between recipient size and donor mass and time posttransplantation.

Rejection
Hyperacute rejection occurs immediately when the kidney is transplanted and is caused by preformed antibodies against the donor HLA, ABO, or other antigens. Hyperacute rejection is rare. The only treatment is removal of the graft.

Acute cellular rejection needs to be identified and treated early. Diagnosis of acute rejection in the very young transplant recipient is often not straightforward. Because most small children receive adult-size kidneys, an elevation in serum creatinine may be a late sign of rejection as a result of the large renal reserve compared with the body mass. Thus, significant allograft dysfunction may be present with little or no increase in the serum creatinine level. One of the earliest and most sensitive signs of rejection is the development of hypertension along with low-grade fever. In children, any increase in serum creatinine, especially if it is accompanied by hypertension, should be considered a symptom of acute rejection until proved otherwise. Late diagnosis and treatment of rejection are associated with a higher incidence of resistant rejections and graft loss. Genomic studies in pediatric kidney transplantation have demonstrated molecular heterogeneity for different acute rejection episodes, not distinguishable by pathologic grading, but with a key established role for B cells as antigen-presenting cells for aggressive T-cell–mediated recalcitrant rejection.

Chronic rejection is the leading cause of graft loss and primarily results from immune and nonimmune injuries such as hypertension, diabetes, and hyperlipidemia. Children often have a gradual decline in their renal function and often have fixed proteinuria and hypertension. Despite initial excitement about the potential of MMF and sirolimus mitigating chronic graft injury, this has not translated readily into observable clinical benefits. Humoral immunity, relating the generation of posttransplant donor-specific anti-HLA antibodies, has been implicated in this injury; attention has also shifted to evaluating the impact of non-HLA antibodies after organ transplantation, as direct mediators of organ injury.

Graft Survival
Five yr graft survival is higher in living-donor recipients compared to grafts from deceased donors. The OPTN/SRTR 2007 annual report gives graft survival at 5 yr (2000-2005) for living-donor kidney transplant as 88.0% for recipients 1-5 yr of age, 84.6% for those 6-10 yr of age, and 74.4% for those 11-17 yr of age. Survival in deceased-donor recipients was 74.4% for those 1-5 yr of age, 72.1% for those 6-10 yr of age, and 63% for those 11-17 yr of age.

From the NAPRTCS data, graft survival rates of pediatric kidney transplants have improved since 1987 with 1 yr survival rates during 2003-2006 of 95.7% for living-donor transplants and 95%
for deceased-donor transplants. Children <10 yr of age have the best long-term graft and patient survival rates of all transplant recipients. Graft survival in adolescent patients is the lowest of all the age groups. It is well known that noncompliance is a difficult problem in this age group. Other risk factors for graft failure are race, previous transplant history, history of multiple blood transfusions, HLA-B matches, sex, and transplant year. Approximately 25% of pediatric kidney transplants are preemptive. Graft survival for living and deceased-donor kidneys is significantly better in the preemptive group compared to patients who are on dialysis first. The 3 most common causes of graft failure are chronic rejection of graft (34.9%), acute rejection of graft (13%), and vascular thrombosis (10.1%). Approximately 6.4% of patients had graft failure as a result of recurrence of primary disease (NAPRTCS 2007). The NAPRTCS 2003-2007 data showed the probability of the first rejection at 12 mo being 8.7% for the living donor and 17.7% for the deceased donor.

Graft survival is significantly worse in the presence of ATN in either donor group. ATN is defined by NAPRTCS as requiring the use of dialysis within the first transplant week. NAPRTCS 2008 data report a 5.1% delay in graft function in living-donor renal transplants compared to the ATN rate of 16.4% in children who received deceased-donor transplants.

**COMPLICATIONS WITH IMMUNOSUPPRESSION INFECTIONS**

Since the mid-1990s, the incidence of acute rejection has decreased but the incidence of infections after transplantation has been increasing.

Pneumonia and urinary tract infection are the most common post-transplant bacterial infections. Urinary tract infections can progress rapidly to urosepsis and may be confused with episodes of acute rejection. Trimethoprim-sulfamethoxazole is used for urinary tract infection antibiotic prophylaxis as well as *Pneumocystis carinii* pneurnonia prophylaxis for at least the first 6 mo after transplant. Opportunistic infections associated with unusual organisms usually do not occur until after the first month after transplantation.

The **herpesviruses** (cytomegalovirus, herpesvirus, varicella-zoster virus, and EBV) pose a special problem in view of their common occurrence in children. Many young children have not yet been exposed to these viruses, and because they lack protective immunity, their predisposition to serious primary infection is high. The incidence of cytomegalovirus seropositivity is approximately 30% in children >5 yr of age and rises to approximately 60% in teenagers. Thus, the younger child is at a greater potential risk for serious infection when a cytomegalovirus-positive donor kidney is transplanted. About half the children are seronegative for EBV, and infection occurs in approximately 75% of these patients. Most EBV infections are clinically silent. PTLD in children may be related to EBV infection in the presence of vigorous immunosuppression. The incidence of these infections is higher in children who receive antibody induction therapy and after treatment of acute rejection. It has also been shown in children that subclinical replication of these viruses is much higher in regimens with maintenance steroids, versus protocols with complete steroid avoidance, and that even subclinical viral replication can have a detrimental effect on the incidence of acute rejection and graft function. Antiviral prophylaxis with ganciclovir and valganciclovir for 3-12 mo after transplantation, especially in the higher-risk groups (recipient-negative, donor-positive), have been effective in reducing the incidence of clinical cytomegalovirus disease. Serial surveillance for these viruses by quantitative polymerase chain reaction for viral load in the peripheral blood has also allowed educated minimization of immunosuppression with resultant reduction in viral burden.

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**Figure 536-1** Surveillance for cytomegalovirus and Epstein-Barr virus infections after pediatric kidney transplantation.
Renal Transplantation

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Chapter 536

Polyomavirus nephropathy is an important cause of allograft dysfunction; almost 30% of children have BK viruria, although allograft dysfunction is observed in lower numbers (∼5%). The increased incidence of polyomavirus nephropathy is thought to be the result of more-potent immunosuppressive regimens. A renal biopsy, with identification of polyoma by immunoperoxidase staining, may be required to make the diagnosis with certainty. Reducing immunosuppression is the main form of therapy, and cidofovir and leflunomide are used as adjunctive therapies.

It is important to monitor for PTLD with routine examinations for lymphadenopathy, hepatosplenomegaly, and EBV screen. Figure 536-1 provides a schematic plan to monitor for EBV, cytomegalovirus, and PTLD.

Hypertension, hyperlipidemia, and posttransplant diabetes mellitus are other potential complications of immunosuppressant medications that need to be monitored for and treated when necessary.

Nonadherence with immunosuppressive medications is one of the most important and most elusive problems facing the medical team. At least half of the pediatric deceased-donor transplant recipients demonstrated significant medication nonadherence in the posttransplantation period by using as an assessment direct reporting to the medical team. This figure exceeded 60% in adolescents. Because direct reporting of nonadherence can significantly underestimate its true incidence, this analysis points out the potential magnitude of the problem. Nonadherence appears to be the principal cause of graft loss in 10-15% of all pediatric kidney transplant recipients; for patients with retransplants, this figure might exceed 25%. Risk factors that suggest an increased propensity toward medication nonadherence include female sex, adolescent age, family instability, insufficient emotional support, lower social economic class, and maladaptive behavior.

Although growth improves after transplantation, chronic steroid use does not allow a child to reach full potential height. The precise mechanism by which steroids impair skeletal growth is unknown. Steroids could reduce the release of growth hormone, reduce insulin growth factor activity, impair growth cartilage directly, decrease calcium absorption, or increase renal phosphate wasting. The use of recombinant human growth hormone in pediatric renal transplant recipients significantly improves growth velocity and standard deviation score (SDS). An allograft GFR of <60 mL/min/1.73 m² is associated with poor growth and low insulin growth factor levels; optimal growth occurs with a GFR >90 mL/min/1.73 m². Graft function is the most important factor after a high corticosteroid dosage in the genesis of posttransplantation growth failure. Steroid minimization and withdrawal protocols have demonstrated growth benefits, and the steroid-avoidance data in children show significant catch-up growth at 5 yr after transplantation. These factors have even greater weight than for age-matched, and gender-matched peers. It is thus likely that with a well-functioning kidney and no maintenance steroids, children might now be able to realize their full height potential.

LONG-TERM OUTCOME

With advances in transplant care and treatment modalities and with diligent attention to the pediatric patient's psychosocial, educational, vocational, and developmental rehabilitation, the social and emotional functioning of the child and the child's family appears to return to preillness levels within 1 yr of successful transplantation. Renal transplantation leads to improvement in linear growth in children. School function tests improve after renal transplantation. Most patients can reenter school and social activities after a short recovery time of 4-6 wk after surgery. A 3 yr follow-up shows that nearly 90% of children are in their appropriate school or job placement positions. Surveys of 10 year survivors of pediatric kidney transplants report that most patients consider their health to be good, and they engage in appropriate social, educational, and sexual activities while experiencing a very good to excellent quality of life.

Bibliography is available at Expert Consult.
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RENAL AGENESIS

Renal agenesis, or absent kidney development, can occur secondary to a defect of the wolffian duct, ureteric bud, or metanephric blastema. Unilateral renal agenesis has an incidence of 1 in 450-1,000 births. Unilateral renal agenesis often is discovered during the course of an evaluation for other congenital anomalies (VACTERL [vertebral defects, imperforate anus, congenital heart disease, tracheoesophageal fistula, renal and limb defects] syndrome; e.g., see Chapter 344). Its incidence is increased in newborns with a single umbilical artery. In true agenesis, the ureter and the ipsilateral bladder hemitrigone are absent. The contralateral kidney undergoes compensatory hypertrophy, to some degree prenatally but primarily after birth. Approximately 15% of these children have contralateral vesicoureteral reflux, and most males have an ipsilateral absent vas deferens because the wolffian duct is absent. Because the wolffian and müllerian ducts are contiguous, müllerian abnormalities in girls also are common. The Mayer-Rokitansky-Küster-Hauser syndrome (1 in 4,000-1 in 10,000 female births) is a group of associated findings that may include vaginal aplasia, uterine maldevelopment, and normal ovaries. Two types are described—type I and type II. In type II, renal anomalies, for example, unilateral renal agenesis or a horseshoe kidney, are common, and skeletal anomalies are present in 10% (see Chapter 554).

Renal agenesis is distinguished from aplasia, in which a nubbin of nonfunctioning tissue is seen capping a normal or abnormal ureter. This distinction may be difficult but usually is clinically insignificant. Unilateral renal agenesis is diagnosed in some patients based on the finding of an absent kidney on ultrasonography or renal scintigraphy (renal scan). Some of these patients were born with a hypoplastic kidney or a multicystic dysplastic kidney that underwent complete cyst regression. Although the specific diagnosis is not critical, if the finding of an absent kidney is based on an ultrasonogram, a functional imaging study such as an MR urogram or renal scan should be performed because some of these patients have an ectopic kidney in the pelvis. If there is a normal contralateral kidney, long-term renal function usually remains normal.

Bilateral renal agenesis is incompatible with extrauterine life and produces the Potter syndrome. Death occurs shortly after birth from pulmonary hypoplasia. The newborn has a characteristic facial appearance, termed Potter facies (Fig. 537-1). The eyes are widely separated with epicanthic folds, the ears are low set, the nose is broad and compressed flat, the chin is receding, and there are limb anomalies. Bilateral renal agenesis should be suspected when maternal ultrasonography demonstrates oligohydramnios, nonvisualization of the bladder, and absent kidneys. The incidence of this disorder is 1 in 3,000 births, with a male predominance, and represents 20% of newborns with the Potter phenotype. Other common causes of neonatal renal failure associated with the Potter phenotype include cystic renal dysplasia and obstructive uropathy. Less-common causes are autosomal recessive polycystic kidney disease (infantile), renal hypoplasia, and medullary dysplasia. Neonates with bilateral renal agenesis die of pulmonary insufficiency from pulmonary hypoplasia rather than renal failure (see Chapter 101).

The term familial renal dysplasia describes families in which renal agenesis, renal dysplasia, multicystic kidney (dysplasia), or a combination, occurs in a single family. This disorder has an autosomal dominant inheritance pattern with a penetrance of 50-90% and variable expression. Because of this association, some clinicians advise screening 1st-degree relatives of persons who have renal agenesis or dysplasia, but this is not standard practice.

Whether persons with a solitary kidney should avoid contact sports such as football and karate is unresolved. The arguments favoring participation are that there are other solitary organs (spleen, liver, and brain) that do not preclude participation in contact sports, and there have been only a few reports of persons losing a kidney from sports injuries. The arguments against such participation are that the contralateral normal kidney is hypertrophic and not as well protected by the ribs, and a serious renal injury could have serious lifelong consequences. The American Academy of Pediatrics recommends an “individual assessment for contact, collision, and limited-contact sports.”
present, the term hypodysplasia is preferred. The term dysplasia is technically a histologic diagnosis and refers to focal, diffuse, or segmentally arranged primitive structures, specifically primitive ductal structures, resulting from abnormal metanephric differentiation. Nonrenal elements, such as cartilage, also may be present. The condition can affect all or only part of the kidney. If cysts are present, the condition is termed cystic dysplasia. If the entire kidney is dysplastic with a preponderance of cysts, the kidney is referred to as a multicystic dysplastic kidney (MCDK) (Fig. 537-2).

The pathogenesis of dysplasia is multifactorial. The “bud” theory proposes that if the ureteral bud arises in an abnormal location, such as an ectopic ureter, there is abnormal penetration and induction of the metanephric blastema, which causes abnormal kidney differentiation, resulting in dysplasia. Renal dysplasia also can occur with severe obstructive uropathy early in gestation, as with the most severe cases of posterior urethral valves or in an MCDK, in which a portion of the ureter is absent or atretic.

MCDK is a congenital condition in which the kidney is replaced by cysts and does not function; it can result from ureteral atresia. Kidney size is highly variable. The incidence is approximately 1 in 2,000. Some clinicians incorrectly use the terms multicystic kidney and polycystic kidney interchangeably. However, polycystic kidney disease is an inherited disorder that may be autosomal recessive or autosomal dominant and affects both kidneys (see Chapter 521). MCDK usually is unilateral and generally is not inherited. Bilateral MCDKs are incompatible with life.

MCDK is the most common cause of an abdominal mass in the newborn, but the vast majority are nonpalpable at birth. In most cases, it is discovered incidentally during prenatal sonography. In some patients, the cysts are identified prenatally, but the cysts regress in utero and no kidney is identified on imaging at birth. Contralateral hydronephrosis is present in 5–10% of patients. Sonography shows the characteristic appearance of a kidney replaced by multiple cysts of varying sizes that do not communicate, and no identifiable parenchyma is present. In the past, most cases were confirmed with a renal scan, which should demonstrate nonfunction. However, presently the diagnosis of MCDK is usually straightforward based on the renal ultrasound, and a scan generally is unnecessary. In some patients, usually boys, a small nonobstructing ureterocele is present in the bladder (see Chapter 540). Although 15% have contralateral vesicoureteral reflux, it is usually low grade, and obtaining a voiding cystourethrogram also is unnecessary, unless there is significant contralateral hydronephrosis or the child develops an upper urinary tract infection. Management is controversial. Complete cyst regression occurs in nearly half of MCDKs by age 7 yr. The risk of associated hypertension is 0.2–1.2%, and the risk of Wilms tumor arising from an MCDK is approximately 1 in 1,200. Because neoplasms arise from the stromal rather than the cystic component, even if the cysts regress completely, the likelihood that the kidney could develop a neoplasm is not altered.

Because of the occult nature of these potential problems, many clinicians advise annual follow-up with sonography and blood pressure measurement. The most important aspect of follow-up is being certain that the solitary kidney is functioning normally. If there is an abdominal mass, the cysts enlarge, the stromal core increases in size, or hypertension develops, nephrectomy is recommended. In lieu of follow-up screening, laparoscopic nephrectomy may be performed.

Renal hypoplasia refers to a small nondysplastic kidney that has fewer than the normal number of calyces and nephrons. The term encompasses a group of conditions with an abnormally small kidney and should be distinguished from aplasia, in which the kidney is rudimentary. If the condition is unilateral, the diagnosis usually is made incidentally during evaluation for another urinary tract problem or hypertension. Bilateral hypoplasia usually manifests with signs and symptoms of chronic renal failure and is a leading cause of end-stage renal disease during the 1st decade of life. A history of polyuria and polydipsia is common. Urinalysis results may be normal. In a rare form of bilateral hypoplasia called oligomeganephronia, the number of nephrons is markedly reduced and those present are markedly hypertrophied.

The Ask-Upmark kidney, also termed segmental hypoplasia, refers to small kidneys, usually weighing not more than 35 g, with 1 or more

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**Figure 537-1** Stillborn infant with renal agenesis exhibiting characteristic Potter facies.

**Figure 537-2** A, Prenatal sonogram demonstrating multicystic dysplastic kidney. B, Surgical specimen.
Upper urinary tract anomalies are more common in children with certain physical findings. The incidence of renal anomalies is increased if there is a single umbilical artery and an abnormality of another organ system (congenital heart disease). External ear anomalies (particularly if the child has multiple congenital anomalies), imperforate anus, and scoliosis are associated with renal anomalies. Infants with these physical findings should undergo a renal sonogram.

Bibliography is available at Expert Consult.

**Figure 537-3** Crossed renal ectopia. Intravenous urography shows both renal collecting systems to the left of the spine. Segmentation anomalies of the sacrum, which are subtle in this child, are one of the skeletal anomalies associated with renal ectopia. (From Slovis T, editor: Caffey’s pediatric diagnostic imaging, ed 11, vol 2, Philadelphia, 2008, Mosby, Fig. 145-23A, p. 2244.)

**Figure 537-4** Horseshoe kidney.

**ASSOCIATED PHYSICAL FINDINGS**

Deep grooves on the lateral convexity, underneath which the parenchyma consists of tubules resembling those in the thyroid gland. It is unclear whether the lesion is congenital or acquired. Most patients are 10 yr or older at diagnosis and have severe hypertension. Nephrectomy usually controls the hypertension.

**ANOMALIES IN SHAPE AND POSITION**

During renal development the kidneys normally ascend from the pelvis into their normal position behind the ribs. The normal process of ascent and rotation of the kidney may be incomplete, resulting in renal ectopia or nonrotation. The ectopic kidney may be in a pelvic, iliac, thoracic, or contralateral position. If the ectopia is bilateral, in 90% of persons the 2 kidneys fuse. The incidence of renal ectopia is approximately 1 in 900 (Fig. 537-3).

Renal fusion anomalies are more common. The lower poles of the kidneys can fuse in the midline, resulting in a horseshoe kidney (Fig. 537-4); the fused portion is termed the isthmus and may be thick functioning parenchyma or a thin fibrous strand. Horseshoe kidneys occur in 1 in 400-500 births but are seen in 7% of patients with Turner syndrome. Horseshoe kidney is one of the many renal anomalies that occur in 30% of patients with Turner syndrome (see Chapter 586). Wilms tumors are 4 times more common in children with horseshoe kidneys than in the general population. Stone disease and hydronephrosis secondary to ureteropelvic junction obstruction are other potential late complications. The incidence of MCDK affecting 1 of the 2 sides of a horseshoe kidney also appears to be increased. With crossed fused ectopia, 1 kidney crosses over to the other side and the parenchyma of the 2 kidneys is fused. Renal function usually is normal. In the most common finding, the left kidney may cross over and fuse with the lower pole of the right kidney. The insertion of the ureter to the bladder does not change, and the adrenal glands remain in their normal positions. The clinical significance of this anomaly is that if renal surgery is necessary, the blood supply is variable and can make partial nephrectomy more difficult.
Bibliography


Urinary tract infections (UTIs) occur in 1% of boys and 1-3% of girls. The prevalence of UTIs varies with age. During the 1st yr of life, the male:female ratio is 2.8-5.4:1. Beyond 1-2 yr, there is a female preponderance, with a male:female ratio of 1:10. In boys, most UTIs occur during the 1st yr of life; UTIs are much more common in uncircumcised boys, especially in the 1st yr of life. In girls, the first UTI usually occurs by the age of 5 yr, with peaks during infancy and toilet training.

UTIs are caused primarily by colonic bacteria. In girls, 75-90% of all infections are caused by Escherichia coli (see Chapter 200), followed by Klebsiella spp. and Proteus spp. (see Chapter 109). Although E. coli is also the most common organism in males, some series report that in boys older than 1 yr of age, Proteus is as common a cause as E. coli; others report a preponderance of Gram-positive organisms in boys. Staphylococcus saprophyticus and enterococcus are pathogens in both
UTIs have been considered a risk factor for the development of renal insufficiency or end-stage renal disease in children, although some have questioned the importance of UTI as an isolated risk factor, because only 2% of children with renal insufficiency report a history of UTI. This paradox may be secondary to better recognition of the risks of UTI and prompt diagnosis and therapy. Furthermore, many children receive antibiotics for fever without a specific diagnosis (e.g., treating a questionable otitis media) resulting in a partially treated UTI.

**CLINICAL MANIFESTATIONS AND CLASSIFICATION**

The 3 basic forms of UTI are pyelonephritis, cystitis, and asymptomatic bacteriuria. Focal pyelonephritis (“nephronia”) and renal abscesses are less common.

**Clinical Pyelonephritis**

Clinical pyelonephritis is characterized by any or all of the following: abdominal, back, or flank pain; fever; malaise; nausea; vomiting; and, occasionally, diarrhea. Fever may be the only manifestation. Newborns can show nonspecific symptoms such as poor feeding, irritability, jaundice, and weight loss. Pyelonephritis is the most common serious bacterial infection in infants younger than 24 mo of age who have fever without an obvious focus (see Chapter 177). These symptoms are an indication that there is bacterial involvement of the upper urinary tract. Involvement of the renal parenchyma is termed acute pyelonephritis, whereas if there is no parenchymal involvement, the condition may be termed pyelitis. Acute pyelonephritis can result in renal injury, termed pyelonephritic scarring.

Acute lobar nephronia (acute lobar nephritis) is a renal mass caused by acute focal infection without liquefaction. It may be an early stage in the development of a renal abscess. Manifestations are identical to pyelonephritis; renal imaging demonstrates the abnormality (Fig. 538-1). Renal abscess can occur following a pyelonephritic infection caused by the usual uropathogens or may be secondary to hematogenous infection (Staphylococcus aureus). Perinephric abscess (Fig. 538-2) can occur secondary to contiguous infection in the perirenal area (e.g., vertebral osteomyelitis, psoas abscess) or pyelonephritis that dissects to the renal capsule.

**Cystitis**

Cystitis indicates that there is bladder involvement; symptoms include dysuria, urgency, frequency, suprapubic pain, incontinence, and mal-
cystitis with hematuria. On imaging, typically there are multiple solid bladder masses that consist histologically of inflammatory infiltrates with eosinophils. Ureteral dilation with hydronephrosis also is common. Children with eosinophilic cystitis may have been exposed to an allergen. Bladder biopsy often is necessary to exclude a neoplastic process. Treatment usually includes antihistamines and nonsteroidal antiinflammatory agents.

**Interstitial cystitis** is characterized by irritative voiding symptoms such as urgency, frequency, and dysuria, and bladder and pelvic pain relieved by voiding with a negative urine culture. The disorder is most likely to affect adolescent girls and is idiopathic. Diagnosis is made by cystoscopic observation of mucosal ulcers with bladder distention. Treatments have included bladder hydrodistention and laser ablation of ulcerated areas, but no treatment provides sustained relief.

**Asymptomatic Bacteriuria**

Asymptomatic bacteriuria refers to a condition in which there is a positive urine culture without any manifestations of infection. It is most common in girls. The incidence is <1% in preschool and school-age girls and is rare in boys. This condition is benign and does not cause renal injury, except in pregnant women, in whom asymptomatic bacteriuria, if left untreated, can result in a symptomatic UTI. Some girls are mistakenly identified as having asymptomatic bacteriuria, whereas they actually are experiencing day or night incontinence or perineal discomfort secondary to UTI; these patients should undergo antibiotic therapy.

### PATHOGENESIS AND PATHOLOGY

Nearly all UTIs are ascending infections. The bacteria arise from the fecal flora, colonize the perineum, and enter the bladder via the urethra. In uncircumcised boys, the bacterial pathogens arise from the flora beneath the prepuce. In some cases, the bacteria causing cystitis ascend to the kidney to cause pyelonephritis. Rarely, renal infection occurs by hematogenous spread, as in endocarditis or in some neonates.

If bacteria ascend from the bladder to the kidney, acute pyelonephritis can occur. Normally the simple and compound papillae in the kidney have an antireflux mechanism that prevents urine in the renal pelvis from entering the collecting tubules. However, some compound papillae, typically in the upper and lower poles of the kidney, allow intrarenal reflux. Infected urine then stimulates an immunologic and inflammatory response. The result can cause renal injury and scarring (Figs. 538-3 and 538-4). Children of any age with a febrile UTI can have acute pyelonephritis and subsequent renal scarring, but the risk is highest in those younger than 2 yr of age.

Table 538-1 lists the host risk factors for UTI. Vesicoureteral reflux is discussed in Chapter 539. If there is grade III, IV, or V vesicoureteral reflux and a febrile UTI, 90% have evidence of acute pyelonephritis on renal scintigraphy or other imaging studies. In girls, UTIs often occur at the onset of toilet training because of bladder/bowel dysfunction that occurs at that age. The child is trying to retain urine to stay dry, yet the bladder may have uninhibited contractions forcing urine out. The result may be high-pressure, turbulent urine flow or incomplete bladder emptying, both of which increase the likelihood of bacteriuria. Bladder/bowel dysfunction can occur in the toilet-trained child who voids infrequently. Similar problems can arise in school-age children who refuse to use the school bathroom. Obstructive uropathy resulting in hydronephrosis increases the risk of UTI because of urinary stasis. Urethral catheterization for urine output monitoring or during a voiding cystourethrogram or nonsterile catheterization can infect the bladder with a pathogen. Constipation with fecal impaction can increase the risk of UTI because it can cause bladder dysfunction.

The pathogenesis of UTI is based in part on the presence of bacterial pili or fimbriae on the bacterial surface. There are 2 types of fimbriae, type I and type II. Type I fimbriae are found on most strains of *E. coli*. Because attachment to target cells can be blocked by d-mannose, these fimbriae are referred to as mannose sensitive. They have no role in pyelonephritis. The attachment of type II fimbriae is not inhibited by mannose, and these are known as mannose resistant. These fimbriae

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**Table 538-1 Risk Factors for Urinary Tract Infection**

| Female gender | Tight clothing (underwear) |
| Uncircumcised male | Pinworm infestation |
| Vesicoureteral reflux* | Constipation |
| Toilet training | Bacteria with P fimbriae |
| Voiding dysfunction | Anatomic abnormality (labial adhesion) |
| Obstructive uropathy | Neuropathic bladder |
| Urethral instrumentation | Sexual activity |
| Wiping from back to front in girls | Pregnancy |
| Bubble bath? | |

*Risk increased for clinical pyelonephritis, not cystitis.*
are expressed by only certain strains of *E. coli*. The receptor for type II fimbriae is a glycosphingolipid that is present on both the uroepithelial cell membrane and red blood cells. The Gal 1-4 Gal oligosaccharide fraction is the specific receptor. Because these fimbriae can agglutinate by P blood group erythrocytes, they are known as P fimbriae. Bacteria with P fimbriae are more likely to cause pyelonephritis. Between 76% and 94% of pyelonephritogenic strains of *E. coli* have P fimbriae, compared with 19–23% of cystitis strains.

Other host factors for UTI include anatomic abnormalities precluding normal micturition, such as a labial adhesion. This lesion acts as a barrier and causes vaginal voiding. A neuropathic bladder can predispose to UTIs if there is incomplete bladder emptying and/or detrusor–sphincter dyssynergia. Sexual activity is associated with UTIs in girls, in part because of incomplete bladder emptying. From 4–7% of pregnant women have asymptomatic bacteriuria, which can develop into a symptomatic UTI. The incidence of UTI in infants who are breastfed is lower than in those fed with formula.

### DIAGNOSIS

UTI may be suspected based on symptoms or findings on urinalysis, or both; a *urine culture is necessary for confirmation and appropriate therapy*. There are several ways to obtain a urine sample; some are more accurate than others. In toilet-trained children, a midstream urine sample usually is satisfactory; the introitus should be cleaned before obtaining the specimen. In uncircumcised boys, the prepucce must be retracted; if the prepuce is not retractable, a voided sample may be unreliable and contaminated with skin flora. According to the 2011 American Academy of Pediatrics (AAP) Clinical Guideline for children 2–24 mo, in children who are not toilet trained, a catheterized or suprapubic aspirate urine sample should be obtained. Alternatively, the application of an adhesive, sealed, sterile collection bag after disinfection of the skin of the genitals can be useful only if the culture is negative or if a single uropathogen is identified. However, a positive culture can result from skin contamination, particularly in girls and uncircumcised boys. If treatment is planned immediately after obtaining the urine culture, a bagged specimen should not be the method because of a high rate of contamination, often with mixed organisms. A suprapubic aspirate generally is unnecessary.

Nitrites and leukocyte esterase usually are positive in infected urine. Microscopic hematuria is common in acute cystitis, but microhematuria alone does not suggest UTI. White blood cell casts in the urinary sediment suggest renal involvement, but in practice these are rarely seen. If the child is asymptomatic and the urinalysis result is normal, their elevation does not prove that the child has acute pyelonephritis. With a renal abscess, the white blood cell count is markedly elevated to >20,000-25,000/mm³. An elevated serum procalcitonin level is associated with pyelonephritis and a high risk of renal scarring. Because sepsis is common in pyelonephritis, particularly in infants and in any child with obstructive uropathy, blood cultures should be drawn before starting antibiotics if possible.

According to the 2011 AAP Guidelines for children 2–24 mo, risk factors for girls include white race, age younger than 12 mo, temperature >39°C (102.2°F), fever for longer than 2 days, and absence of another source of infection. Risk factors for boys include nonblack race, temperature >39°C (102.2°F), fever for longer than 24 hr, and absence of another source of infection. Atypical features include failure to respond within 48 hr of appropriate antibiotics, poor urine flow, an abdominal flank or suprapubic mass, non–*E. coli* pathogen, urosepsis, and an elevated creatinine level.

### TREATMENT

Acute cystitis should be treated promptly to prevent possible progression to pyelonephritis. If the symptoms are severe, presumptive treatment is started pending results of the culture. If the symptoms are mild or the diagnosis is doubtful, treatment can be delayed until the results of culture are known, and the culture can be repeated if the results are uncertain. If treatment is initiated before the results of a culture and sensitivities are available, a 3- to 5-day course of therapy with trimethoprim-sulfamethoxazole (TMP-SMX) or trimethoprim is effective against many strains of *E. coli*. Nitrofurantoin (5–7 mg/kg/24 hr in 3–4 divided doses) also is effective and has the advantage of being active against *Klebsiella* and *Enterobacter* organisms. Amoxicillin (50 mg/kg/24 hr) also is effective as initial treatment but has a high rate of bacterial resistance.

In acute febrile infections suggesting *clinical pyelonephritis*, a 7–14 day course of broad-spectrum antibiotics capable of reaching significant tissue levels is preferable. Children who are dehydrated, are vomiting, are unable to drink fluids, are 1 mo of age or younger, have complicated infection, or in whom urosepsis is a possibility should be admitted to the hospital for IV rehydration and IV antibiotic therapy. Parenteral treatment with ceftriaxone (50–75 mg/kg/24 hr, not to

![Table 538-2: Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAQAAAAbCAYAAAD5mR7EAAAAASUVORK5CYII=)
exceed 2 g) or cefotaxime (100 mg/kg/24 hr), or ampicillin (100 mg/ kg/24 hr) with an aminoglycoside such as gentamicin (3-5 mg/kg/24 hr in 1-3 divided doses) is preferable. The potential ototoxicity and nephrotoxicity of aminoglycosides should be considered; serum creatinine should be obtained before initiating treatment, and daily trough gentamicin levels should be obtained during therapy. Treatment with aminoglycosides is particularly effective against Pseudomonas spp., and alkalinization of urine with sodium bicarbonate increases its effectiveness in the urinary tract.

Oral third-generation cephalosporins such as cefixime are as effective as parenteral ceftriaxone against a variety of Gram-negative organisms other than Pseudomonas, and these medications are considered by some authorities to be the treatment of choice for oral outpatient therapy. Nitrofurantoin should not be used routinely in children with a febrile UTI because it does not achieve significant renal tissue levels. The oral fluoroquinolone ciprofloxacin is an alternative agent for resistant microorganisms, particularly Pseudomonas, in patients older than age 17 yr. It also has been used on occasion for short-course therapy in younger children with Pseudomonas UTI. Levofloxacin is an alternative quinolone with a good safety profile in children. However, the clinical use of fluoroquinolones in children should be used with caution because of potential cartilage damage. In some children with a febrile UTI, intramuscular injection of a loading dose of ceftriaxone followed by oral therapy with a third-generation cephalosporin is effective. A urine culture 1 wk after the termination of treatment of a UTI ensures that the urine is sterile but is not routinely needed. A urine culture during treatment almost invariably is negative.

Children with a renal or perirenal abscess or with infection in obstructed urinary tracts can require surgical or percutaneous drainage in addition to antibiotic therapy and other supportive measures (see Fig. 538-2). Small abscesses may initially be treated without drainage.

In a child with recurrent UTIs, identification of predisposing factors is beneficial. Many school-age girls have bladder–bowel dysfunction (see Chapter 543); treatment of this condition often reduces the likelihood of recurrent UTI. Some children with UTIs void infrequently, and many also have severe constipation (see Chapters 306 and 332). Behavioral modification, with treatment of constipation as described in Chapter 543, often is effective. Antimicrobial prophylaxis using trimethoprim or nitrofurantoin at 30% of the normal therapeutic dose once a day is another approach to this problem but is unnecessary in most children with recurrent UTIs in the absence of severe reflux. Prophylaxis with TMP-SMZ, amoxicillin, or cephalexin can also be effective, but the risk of breakthrough UTI may be higher because bacterial resistance may be induced. Urologic conditions for recurrent UTIs that might benefit from long-term prophylaxis include neuropathic bladder, urinary tract stasis and obstruction, severe vesicoureteral reflux (see Chapter 539), and urinary calculi. There is interest in probiotic therapy, which replaces pathologic urogenital flora, and cranberry juice, which prevents bacterial adhesion and biofilm formation, but these agents have not proved beneficial in preventing UTI in children.

The main consequences of chronic renal damage caused by pyelonephritis are arterial hypertension and end-stage renal insufficiency; when they are found they should be treated appropriately (see Chapters 445 and 535).

**IMAGING STUDIES IN CHILDREN WITH A FEBRILE UTI**

The goal of imaging studies in children with a UTI is to identify anatomic abnormalities that predispose to infection, determine whether there is active renal involvement, and to assess whether renal function is normal or at risk.

There are 2 historical approaches to imaging, the traditional “bottom-up” and the “top-down” approaches.

1. The “bottom-up” method was a renal sonogram plus voiding cystourethrogram; this approach will identify upper and lower urinary tract abnormalities, including vesicoureteral reflux, bladder–bowel dysfunction, and bladder abnormalities, such as a paraureteral diverticulum. It is unlikely to detect renal scarring unless it is significant (renal cortical irregularity, small kidney on renal ultrasound). A dimercaptosuccinic acid (DMSA) scan is necessary to provide the best assessment of renal scarring.

   In some centers, the voiding cystourethrogram (VCUG) is delayed for 2-6 wk to allow inflammation in the bladder to resolve; however, the incidence of reflux is identical, regardless of whether the VCUG is obtained acutely at the time of treatment of the UTI or after 6 wk. Obtaining the VCUG before the child is discharged from the hospital is appropriate and ensures that the evaluation is complete. If available, a radionuclide VCUG rather than a contrast VCUG can be used in girls; this technique causes less radiation exposure to the gonads than does the contrast study. However, the radioisotope VCUG does not provide anatomic definition of the bladder, allow precise grading of reflux, demonstrate a paraureteral diverticulum, or show whether reflux is occurring into a duplicated collecting system or an ectopic ureter. In boys, VCUG definition of the urethra is important to detect posterior urethral valves (see Chapter 504).

2. The “top-down” approach was intended to reduce the number of VCUG examinations. It begins with a DMSA renal scan, to identify areas of acute pyelonephritic involvement, termed acute pyelonephritis (Fig. 538-5). The DMSA scan in younger children generally requires sedation. This condition is characterized by fever, malaise, abdominal or flank pain, and occasionally nausea and vomiting, and is a significant risk factor for renal injury and scarring. On DMSA, involved areas of the kidney are photopenic and the kidney is enlarged. Of children with a febrile UTI, approximately 50% have a positive DMSA scan. Of those with a positive scan, approximately 50% develop renal scarring in the areas of acute pyelonephritis, and in the remainder with acutely positive scans, the renal appearance will normalize. In children with dilating grades of reflux (III, IV, V), 80-90% with a febrile UTI have a DMSA scan consistent with acute pyelonephritis. Children with grades I and II reflux and those without reflux can also develop acute pyelonephritis. In longitudinal studies of children with grades I and II reflux and acute pyelonephritis, the reflux usually resolves. If the DMSA scan is normal during a febrile UTI, no scarring will result from that particular infection. CT is another diagnostic tool that can image acute pyelonephritis, but clinical experience with DMSA is much greater, and CT scans have significant radiation. If the DMSA scan is positive, then a VCUG is performed (Fig. 538-6), because 90% of children with dilating reflux have a positive DMSA scan. If reflux is identified, treatment is based on the perceived long-term risk of the reflux to the child (see Chapter 538). One limitation to this approach is that many hospitals caring for children with a febrile UTI might not have facilities for performing a DMSA scan in children. In these cases, a renal sonogram should be performed, after which the clinician decides whether to send the child to a facility with
DMSA capability or instead do a VCUG. In addition, if the DMSA scan is positive, then a follow-up scan is indicated 4-6 mo later to determine whether renal scarring occurred.

The AAP recommends that in a typical first-episode of UTI, initial imaging should be ultrasonography of the kidneys, ureters, and bladder. VCUG is indicated if the ultrasound study is abnormal, the patient has atypical features, or after a recurrent febrile UTI (Table 538-3).

In children with a history of cystitis, (dysuria, urgency, frequency, suprapubic pain), imaging is usually unnecessary. Instead, assessment and treatment of bladder and bowel dysfunction is important. If there are numerous lower UTIs, then a renal sonogram is appropriate, but a VCUG rarely adds useful information.

The AAP recommendation has resulted in a significant decrease in the number of VCUGs ordered. However, the pediatric urologic community has raised numerous concerns regarding the recommendations, and prospective studies will be necessary before determining whether they should be adopted. One consequence is that many primary care physicians have generalized these recommendations, which were intended for children 2-24 mo, to all children.

Similarly, in 2007, the NICE (National Institute for Health and Clinical Excellence, UK) guidelines for diagnosis, management, and imaging after UTI were released (Table 538-4). These recommendations divided children into those younger than 6 mo, 6 mo-3 yr, and older than 3 yr of age. An initial VCUG is recommended only in children younger than age 6 mo. These recommendations are highly controversial.

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**Table 538-3** Guideline Recommendations for Diagnostic Evaluation Following a Febrile Urinary Tract Infection in Infants

<table>
<thead>
<tr>
<th>GUIDELINE</th>
<th>ULTRASONOGRAPHY</th>
<th>VCUG</th>
<th>LATE DMSA SCAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute for Health And Care Excellence (NICE)*</td>
<td>(see Table 538-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Academy of Pediatrics</td>
<td>Yes</td>
<td>If abnormal ultrasonogram</td>
<td>No</td>
</tr>
<tr>
<td>Italian Society for Paediatric Nephrology (ISPN)</td>
<td>Yes</td>
<td>If abnormal ultrasonogram or if risk factors are present†</td>
<td>If abnormal ultrasonogram or VUR</td>
</tr>
</tbody>
</table>

*Upper urinary tract dilation on ultrasonography, poor urinary flow, infection with organism other than **E. coli**, or family history of vesicoureteral reflux.
†Abnormal antenatal ultrasonogram of fetal urinary tract, family history of reflux, septicemia, renal failure, age younger than 6 mo in a male infant, likely family noncompliance, incomplete bladder emptying, no clinical response to appropriate antibiotic therapy within 72 hr, or infection with organism other than **E. coli**.

**Table 538-4** Recommended Imaging Schedule for Children with Urinary Tract Infection

<table>
<thead>
<tr>
<th>CHILD AGE AND TESTS</th>
<th>TYPE OF INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RESPOND WELL TO TREATMENT WITHIN 48 HR</td>
</tr>
<tr>
<td><strong>CHILDREN YOUNGER THAN 6 MO OLD</strong></td>
<td></td>
</tr>
<tr>
<td>Ultrasound scan during acute infection</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound scan within 6 wk of infection</td>
<td>Yes</td>
</tr>
<tr>
<td>DMSA scan 4-6 mo after acute infection</td>
<td>No</td>
</tr>
<tr>
<td>Micturating cystograms</td>
<td>Consider if ultrasound scan abnormal</td>
</tr>
</tbody>
</table>

| **CHILDREN 6 MO-3 YR OLD** | | | |
| Ultrasound scan during acute infection | No | Yes | No |
| Ultrasound scan within 6 wk of infection | No | No | Yes |
| DMSA scan 4-6 mo after acute infection | No | Yes | Yes |
| Micturating cystograms | | Not routine, consider if dilation on ultrasound, poor urine flow, non-**E. coli** infection, or family history of vesicoureteric reflux | |

| **CHILDREN OLDER THAN AGE 3 YR** | | | |
| Ultrasound scan during acute infection | No | Yes | No |
| Ultrasound scan within 6 wk of infection | No | No | Yes |
| DMSA scan 4-6 mo after acute infection | No | Yes | Yes |
| Micturating cystograms | No | No | No |

DMSA, dimercaptosuccinic acid.
because the methodology was not based on evidence but on expert opinion. In addition, there was no retrospective or prospective assessment of the potential of this approach to identify significant uropathology. There is evidence that a significant number of children with uropathology would not have been identified under these guidelines.

**PROPHYLAXIS OF RECURRENT URINARY TRACT INFECTION**

See Chapter 539.

In children with a first episode of pyelonephritis in an otherwise anatomically normal urinary tract and no evidence of reflux, no antimicrobial prophylaxis is required in an attempt to prevent a recurrence or renal scarring.

_Bibliography is available at Expert Consult._
Bibliography
Vesicoureteral reflux (VUR) describes the retrograde flow of urine from the bladder to the ureter and kidney. The ureteral attachment to the bladder normally is oblique, between the bladder mucosa and detrusor muscle, creating a flap-valve mechanism that prevents VUR (Fig. 539-1). VUR occurs when the submucosal tunnel between the mucosa and detrusor muscle is short or absent. Affecting 1-2% of children, VUR usually is congenital and often is familial. VUR is present in approximately 30% of females who had a urinary tract infection and in 5-15% of infants with antenatal hydronephrosis.

VUR predisposes to kidney infection (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract (see Chapter 538). The inflammatory reaction caused by pyelonephritis can result in renal injury or scarring, also termed reflux-related renal injury or reflux nephropathy. In children with a febrile urinary tract infection (UTI), those with VUR are 3 times more likely to develop renal injury compared to those without VUR. Extensive renal scarring impairs renal function and can result in renin-mediated hypertension (see Chapter 445), renal insufficiency or end-stage renal disease (see Chapter 535), impaired somatic growth, and morbidity during pregnancy. Scarring associated with reflux may be present at birth or develop in the absence of infection.

In the past, reflux nephropathy accounted for as much as 15-20% of end-stage renal disease in children and young adults. With greater attention to the management of UTIs and a better understanding of VUR, end-stage renal disease secondary to reflux nephropathy is uncommon. Reflux nephropathy remains a common cause of hypertension in children. VUR in the absence of infection or elevated bladder pressure (e.g., neuropathic bladder, posterior urethral valves) rarely causes renal injury.

**CLASSIFICATION**

VUR severity is graded using the International Reflux Study Classification of I-V and is based on the appearance of the urinary tract on a contrast voiding cystourethrogram (VCUG) (Figs. 539-2 and 539-3). The higher the VUR grade the greater the likelihood of renal injury. VUR severity is an indirect indication of the degree of abnormality of the ureterovesical junction.

VUR may be primary or secondary (Table 539-1). Bladder–bowel dysfunction can worsen preexisting VUR if there is a marginally competent ureterovesical junction. In the most severe cases, there is such massive VUR into the upper tracts that the bladder becomes...
overdistended. This condition, the megacystis-megaureter syndrome, occurs primarily in boys and may be unilateral or bilateral (Fig. 539-4). Reimplantation of the ureters into the bladder to correct VUR corrects the condition.

Approximately 1 in 125 children have a duplication of the upper urinary tract, in which 2 ureters rather than 1 drain the kidney. Duplication may be partial or complete. In partial duplication, the ureters join above the bladder and there is 1 ureteral orifice. In complete duplication, the attachment of the lower pole ureter to the bladder is superior and lateral to the upper pole ureter. The valve-like mechanism for the lower pole ureter often is marginal, and VUR into the lower ureter occurs in as many as 50% of cases. VUR occurs into both the lower and upper systems in some persons (Fig. 539-5). With a duplication anomaly, some patients have an ectopic ureter, in which the upper pole ureter drains outside the bladder (see Chapters 540 and 543 and Figs. 543-6 and 543-7). If the ectopic ureter drains into the bladder neck, typically it is obstructed and refluxes. Duplication anomalies also are common in children with a ureterocele, which is a cystic swelling of the intramural portion of the distal ureter. These patients often have VUR into the associated lower pole ureter or the contralateral ureter. In addition, generally VUR is present when the ureter enters a bladder diverticulum (Fig. 539-6).

VUR is present at birth in 25% of children with neuropathic bladder, as occurs in myelomeningocele (see Chapter 591.4), sacral agenesis, and many cases of high imperforate anus. VUR is seen in 50% of boys with posterior urethral valves. VUR with increased intravesical pressure (as in detrusor-sphincter dyssynergia or bladder outlet obstruction) can result in renal injury because of increased intravesical pressure transmitted to the upper urinary tract, even in the absence of infection.

Primary VUR occurs in association with several congenital urinary tract abnormalities. Of children with a multicystic dysplastic kidney or renal agenesis (see Chapter 537), 15% have VUR into the contralateral kidney, and 10-15% of children with a ureteropelvic junction obstruction have VUR into either the hydronephrotic kidney or the contralateral kidney.

Table 539-1 Classification of Vesicoureteral Reflux

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CAUSE</th>
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<tbody>
<tr>
<td>Primary</td>
<td>Congenital incompetence of the valvular mechanism of the vesicoureteral junction</td>
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| Primary associated with other malformations of the ureterovesical junction | Ureteral duplication  
Ureterocele with duplication  
Ureteral ectopia  
Paraureteral diverticula |
| Secondary to increased intravesical pressure | Neuropathic bladder  
Nonneuropathic bladder dysfunction  
Bladder outlet obstruction |
| Secondary to inflammatory processes       | Severe bacterial cystitis  
Foreign bodies  
Vesical calculi  
Clinical cystitis |
| Secondary to surgical procedures involving the ureterovesical junction | Surgery |

Figure 539-4 Voiding cystourethrogram in newborn boy with megacystis-megaureter syndrome. Note the massive ureteral dilation caused by high-grade vesicoureteral reflux. The bladder is very distended. There was no urethral obstruction or neuropathic dysfunction.

Figure 539-5 Various anatomic defects of the ureterovesical junction associated with vesicoureteral reflux.

Figure 539-6 VUR and bladder diverticulum. The voiding cystourethrogram demonstrates left vesicoureteral reflux and a paraureteral diverticulum.
VUR (idiopathic) appears to be an autosomal dominant inherited trait with variable penetrance. Approximately 35% of siblings of children with VUR also have VUR, and VUR is found in nearly half of newborn siblings. The likelihood of a sibling having VUR is independent of the grade of VUR or sex of the index child. Approximately 12% of asymptomatic siblings with VUR have evidence of renal scarring. In addition, 50% of children born to women with a history of VUR also have VUR. In 2010 the American Urological Association Vesicoureteral Reflux Guidelines Panel stated that, in siblings of individuals with VUR, a VCUG or radionuclide cystogram is recommended if there is evidence of renal cortical abnormalities or renal size asymmetry on sonography, or if the sibling has a history of UTI. Otherwise, screening is optional. VUR may be suggested on a prenatal ultrasound, which demonstrates dilated renal calyces. Primary VUR is uncommon in African-Americans.

CLINICAL MANIFESTATIONS
VUR usually is discovered during evaluation for a UTI (see Chapter 538). Among these children, 80% are female, and the average age at diagnosis is 2-3 yr. In other children, a VCUG is performed during evaluation of bladder–bowel dysfunction, renal insufficiency, hypertension, or other suspected pathologic process of the urinary tract. Primary VUR also may be discovered during evaluation for antenatal hydronephrosis. In this select population, 80% of affected children are male, and the VUR grade usually is higher than in girls whose VUR is diagnosed following a UTI. The UTI may be symptomatic, an isolated febrile event, or more often both febrile and symptomatic (abdominal pain, dysuria, etc.). Bladder and bowel dysfunction (constipation) may be present in 50% of children with reflux and a UTI.

DIAGNOSIS
Diagnosis of VUR requires catheterization of the bladder, instillation of a solution containing iodinated contrast or a radiopharmaceutical, and radiologic imaging of the lower and upper urinary tract: a contrast VCUG or radionuclide cystogram, respectively. The bladder and upper urinary tracts are imaged during bladder filling and voiding. VUR occurring during bladder filling is termed low-pressure VUR; VUR during voiding is termed high-pressure VUR. VUR in children with low-pressure VUR is significantly less likely to resolve spontaneously than in children who exhibit only high-pressure VUR. Radiation exposure during a radionuclide cystogram is significantly less than that from a contrast VCUG. However, the contrast VCUG provides more anatomic information, such as demonstration of a duplex collecting system, ectopic ureter, paraureteral (bladder) diverticulum, bladder outlet obstruction in boys, upper urinary tract stasis, and signs of voiding dysfunction, such as a “spinning top” urethra in girls. The VUR grading system is based on the appearance on contrast VCUG, and the grade reported is the maximum grade observed during the study. For follow-up evaluation, some prefer the radionuclide cystogram because of the lower radiation exposure (Fig. 539-7), although it is difficult to determine whether the VUR severity has changed.

Children undergoing cystography may be psychologically traumatized by the catheterization. Careful preparation by caregivers, use of Child Life individuals, or administration of oral or nasal midazolam (for sedation and amnesia) or propofol before the study can result in a less-distressing experience.

Indirect cystography is a technique of detecting VUR without catheterization that involves injecting an intravenous radiopharmaceutical that is excreted by the kidneys, waiting for it to be excreted into the bladder, and imaging the lower urinary tract while the patient voids. This technique detects only 75% of VUR cases. Another technique, which avoids radiation exposure, involves instilling sonographic contrast medium through a urethral catheter. The kidneys are imaged sonographically to determine whether any of the material reflexes. This technique is investigational.

After VUR is diagnosed, assessment of the upper urinary tract is important. The goal of upper tract imaging is to assess whether renal scarring and associated urinary tract anomalies are present. Renal imaging typically is performed with a renal sonogram or renal scintigraphy (Fig. 539-8; see Chapter 538).

The child should be evaluated for bladder–bowel dysfunction, including urgency, frequency, diurnal incontinence, infrequent voiding.

Figure 539-7 Radionuclide cystogram shows bilateral VUR.

Figure 539-8 A, Voiding cystourethrogram (VCUG) in a 3 yr old girl with 2 febrile urinary tract infections shows bilateral grade III VUR. B, At 5 yr, repeat VCUG shows worsening VUR and calyceal clubbing, indicating renal scarring. C, At 11 yr, she has developed renin-mediated hypertension. Dimercaptosuccinic acid (DMSA) renal scan shows significant VUR-related renal scarring.
or a combination of these (see Chapter 543). Children with an overactive bladder often undergo a regimen of behavioral modification with timed voiding, and, on occasion, anticholinergic therapy.

After diagnosis, the child’s height, weight, and blood pressure should be measured and monitored. If upper tract imaging shows renal scarring, a serum creatinine measurement should be obtained. The urine should be assessed for infection and proteinuria.

**NATURAL HISTORY**

The incidence of reflux-related renal scarring increases with VUR grade. With bladder growth and maturation, the VUR grade often resolves or improves. Lower grades of VUR are much more likely to resolve than are higher grades. For grades I and II VUR, the likelihood of resolution is similar regardless of age at diagnosis and whether it is unilateral or bilateral. For grade III, a younger age at diagnosis and unilateral VUR usually are associated with a higher rate of spontaneous resolution (Fig. 539-9). Bilateral grade IV VUR is much less likely to resolve than is unilateral grade IV VUR. Grade V VUR rarely resolves. The mean age at VUR resolution is 6 yr.

VUR does not usually cause renal injury in the absence of infection, but in situations with high-pressure VUR, as in children with posterior urethral valves, neuropathic bladder, and nonneurogenic neurogenic bladder (i.e., Hinman syndrome), sterile VUR can cause significant renal damage. Children with high-grade VUR who acquire a UTI are at significant risk for acute and recurrent pyelonephritis and new renal scarring (see Fig. 539-8).

**TREATMENT**

The goals of treatment are to prevent pyelonephritis, VUR-related renal injury, and other complications of VUR. Medical therapy is based on the principle that VUR often resolves over time and that if UTIs can be prevented, the morbidity or complications of VUR may be avoided without surgery. Medical therapy includes observation with behavioral modification or behavioral modification with antimicrobial prophylaxis in some patients. The basis for surgical therapy is that in selected children, ongoing VUR has caused or has significant potential for causing renal injury or other VUR-related complications, and that elimination of VUR minimizes the risk of these problems. Therapy for VUR should be individualized based on a particular patient’s risk factors.

**Observation**

In children undergoing observation, therapeutic emphasis is directed to minimizing the risk of UTI by behavioral modification. These methods include timed voiding during the day, ensuring regular fecal elimination, increased fluid intake, periodic assessment of satisfactory bladder emptying, and prompt assessment and treatment of UTIs, particularly febrile UTIs. This approach is most appropriate for children with grades I and II VUR, and perhaps older children with persistent VUR and normal kidneys who have not experienced clinical pyelonephritis.

**Antimicrobial Prophylaxis**

In the past, based on clinical series demonstrating the effectiveness of antibiotic prophylaxis and the 1997 *American Urological Association* (AUA) Reflux Guidelines, daily prophylaxis was recommended as initial therapy for most children with VUR. Currently, many families express concern regarding the safety and benefit of prophylaxis. In addition, as a result of several prospective clinical trials, the benefit of prophylaxis has been questioned in children with VUR. The risk of recurrent UTI is highest in patients with grade III or IV reflux, those with bowel and bladder dysfunction, and those whose first reflux associated UTI was febrile rather than just symptomatic without fever. Antibiotic prophylaxis after a reflux associated UTI decreases the risk of recurrent UTI but increases the risk of developing resistant bacteria. In one study, antibiotic prophylaxis reduced the risk of new renal scars in children with grade III or IV reflux; while in another larger study antibiotic prophylaxis did not have an effect on the incidence of new renal scars in those with severe reflux (approximately 10% developed new scars regardless of prophylaxis).

**Surgery**

The purpose of surgical therapy is to minimize the risks of ongoing VUR and nonsurgical therapy (prophylaxis and follow-up testing). VUR can be corrected through a lower abdominal or inguinal incision (open), laparoscopically (with or without robotic assistance), or endoscopically with subureteral injection.

Open surgical management involves modifying the abnormal ureterovesical attachment to create a 4:1 to 5:1 ratio of intramural ureter length: ureteral diameter. The operation can be performed from either outside or inside the bladder. When VUR is associated with severe ureteral dilation (i.e., megaureter), the ureter must be tailored or narrowed to a more normal size to allow a smaller length:width ratio for the intramural tunnel, and a corner of the bladder is attached to the psoas tendon, forming a *psoas hitch*. Most children can be discharged 1-2 days following the surgical procedure. If the refluxing kidney is poorly functioning, nephrectomy or nephroureterectomy is indicated. Laparoscopic VUR correction and robotic-assisted laparoscopic ureteral reimplantation have been investigated and have been shown to have similar results to conventional open surgery in older children.

The success rate of conventional open ureteral reimplantation in children with primary VUR is >95-98% for grades I-IV, with 2% experiencing persistent VUR and 1% having ureteral obstruction that requires correction. The success rate is so high that many pediatric urologists do not perform a postoperative VCUG unless the child develops clinical pyelonephritis. For grade V VUR, the success rate is...
approximately 80%. In lower grades of VUR, a failed reimplantation is most likely to occur in children with undiagnosed bladder-bowel dysfunction. In children with secondary VUR (posterior urethral valves, neuropathic bladder), the success rate is slightly lower than with primary VUR. The risk of pyelonephritis in children with grades III and IV VUR is significantly lower following open surgical correction compared with medical management. Surgical repair will not reverse renal scarring or cause improvement in renal function.

Endoscopic repair of VUR involves injection of a bulking agent through a cystoscope just beneath the ureteral orifice, creating an artificial flap-valve (Figs. 539-10 and 539-11). In 2001, the FDA approved the use of a biodegradable material, dextranomer microspheres suspended in hyaluronic acid (Deflux), for subureteral injection. The advantage of subureteral injection is that it is a noninvasive outpatient procedure (performed under general anesthesia) with no recovery time. The success rate is 70-80% and is highest for lower grades of VUR. If the first injection is unsuccessful, 1 or 2 repeat injections can be performed. The VUR recurrence rate is approximately 10%.

**Current Vesicoureteral Reflux Guidelines**

In 2010 the AUA provided updated evidence-based guidelines regarding VUR management, and in 2012 the European Association of Urology published expert opinion based guidelines. Both society recommendations were based on risk assessment of children with VUR.

The long-standing belief regarding the benefit of antibiotic prophylaxis in children with VUR has been questioned. Multiple randomized controlled prospective trials suggested that the risk of UTI in children with VUR is not reduced by prophylaxis. Most of the children in these trials had grades I-III VUR, and few younger than 1 yr old were studied. In contrast, the PRIVENT (Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts) trial from Australia showed significant benefit to prophylaxis in children with VUR. The Swedish VUR Trial in Children studied children younger than 2 yr of age with grades III and IV VUR; they compared antibiotic prophylaxis to observation and endoscopic injection therapy. Girls in the surveillance group had a significantly higher incidence of febrile UTI and new renal scarring compared to the other treatment groups. The largest randomized trial (RIVUR [Randomized Intervention for Children with Vesicoureteral Reflux]) enrolled more than 600 children and demonstrated a reduction in the recurrence rate of UTIs but no reduction of the occurrence of renal scarring with antibiotic prophylaxis.

Prophylaxis is recommended by the AUA in children at greatest risk for VUR-related renal injury (i.e., those younger than 1 yr of age). In addition, evaluation for bladder and bowel dysfunction is considered a standard part of initial and ongoing patient evaluation in children with VUR. Because children with bladder and bowel dysfunction and VUR are much more likely to have recurrent UTIs and renal scarring, prophylaxis is recommended for these children. In children with VUR who are being managed by surveillance, if a febrile UTI occurs, prophylaxis is recommended. The decision whether to recommend observation, medical therapy, or surgery is based on the risk of VUR to the patient, the likelihood of spontaneous resolution, and the parents’ and patient’s preferences, and the family should understand the risks and benefits of each treatment approach.

Another aspect of VUR management pertains to screening. VUR is known to be a familial disorder with autosomal dominant transmission with variable penetrance. The advantage of early VUR detection is to implement treatment before a potentially damaging episode of clinical pyelonephritis. In siblings of an index patient with VUR, optional management includes screening of asymptomatic siblings or offspring with a renal ultrasound or VCUG. The AUA recommends that a VCUG should be obtained if a screening ultrasound demonstrated a renal abnormality or if the sibling had a UTI.

**Figure 539-10** Endoscopic correction of VUR. Through a cystoscope, a needle is inserted into the submucosal plane deep to the ureteral orifice and bulking agent is injected, creating a flap-valve to prevent VUR. (Adapted from Ortenberg J: Endoscopic treatment of vesicoureteral reflux in children, Urol Clin North Am 25:151–156, 1998.)

**Figure 539-11** A, Endoscopic view of right vesicoureteral refluxing ureter. B, The same ureter after subureteral injection of dextranomer microspheres.
The AUA also determined that female newborns with renal pelvic dilation were significantly more likely than male newborns to have VUR. The AUA recommended that a VCUG should be performed in neonates with grade 3-4 antenatal hydronephrosis (moderate to severe pelvocaliceal dilation), hydroureter, or an abnormal bladder. In children with less-severe renal pelvic dilation, an observational approach without screening for VUR, with prompt treatment of any UTI, is appropriate. However, they also indicated that obtaining a VCUG is considered an appropriate option for neonates with lesser grades of hydronephrosis.

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Chapter 539  Vesicoureteral Reflux  2567.e1

Bibliography


Most childhood obstructive lesions are congenital, although urinary tract obstruction can be caused by trauma, neoplasia, calculi, inflammatory processes, or surgical procedures. Obstructive lesions occur at any level from the urethral meatus to the calyceal infundibula (Table 540-1). The pathophysiologic effects of obstruction depend on its level, the extent of involvement, the child's age at onset, and whether it is acute or chronic.

ETIOLOGY

Ureteral obstruction occurring early in fetal life results in renal dysplasia, ranging from multicystic kidney, which is associated with ureteral or pelvic atresia (see Fig. 537-2 in Chapter 537), to various degrees of histologic renal cortical dysplasia that are seen with less-severe obstruction. Chronic ureteral obstruction in late fetal life or after birth results in dilation of the ureter, renal pelvis, and calyces, with alterations of renal parenchyma ranging from minimal tubular changes to dilation of Bowman's space, glomerular fibrosis, and interstitial fibrosis. After birth, infections often complicate obstruction and can increase renal damage.

Prenatal screening with ultrasonography may detect antenatal hydronephrosis, which is graded by the trimester and the anterior-posterior diameter of the renal pelvis (Table 540-2); most are mild. Table 540-3 notes the eventual etiology.

CLINICAL MANIFESTATIONS

Obstruction of the urinary tract generally causes hydronephrosis, which typically is asymptomatic in its early phases. An obstructed kidney secondary to a ureteropelvic junction (UPJ) or ureterovesical junction obstruction can manifest as a unilateral mass or cause upper abdominal or flank pain on the affected side. Pyelonephritis can occur because of urinary stasis. An upper urinary tract stone can occur, causing abdominal and flank pain and hematuria. With bladder outlet obstruction, the urinary stream may be weak; urinary tract infection (UTI; see Chapter 538) is common. Many of these lesions are identified by antenatal ultrasonography; an abnormality involving the genitourinary tract is suspected in as many as 1 in 100 fetuses.

Obstructive renal insufficiency can manifest itself by failure to thrive, vomiting, diarrhea, or other nonspecific signs and symptoms. In older children, infravesical obstruction can be associated with overflow urinary incontinence or a poor urine stream. Acute ureteral obstruction causes flank or abdominal pain; there may be nausea and vomiting. Chronic ureteral obstruction can be silent or can cause vague abdominal or typical flank pain with increased fluid intake.
DIAGNOSIS
Urinary tract obstruction may be diagnosed prenatally by ultrasonography, which typically shows hydronephrosis and occasionally a distended bladder. More complete evaluation, including imaging studies, should be undertaken in these children in the neonatal period.

Urinary tract obstruction is often silent. In the newborn infant, a palpable abdominal mass most commonly is a hydronephrotic or multicystic dysplastic kidney. With posterior urethral valves, which is an infravesical obstructive lesion in boys, a walnut-sized mass representing the bladder is palpable just above the pubic symphysis. A patent draining urachus also can suggest urethral obstruction. Urinary ascites in the newborn usually is caused by renal or bladder urinary extravasation secondary to posterior urethral valves. Infection and sepsis may be the first indications of an obstructive lesion of the urinary tract. The combination of infection and obstruction poses a serious threat to infants and children and generally requires parenteral administration of antibiotics and drainage of the obstructed kidney. Renal ultrasonography should be performed in all children during the acute stage of an initial febrile UTI.

Imaging Studies
Renal Ultrasonography
Hydronephrosis is the most common characteristic of obstruction (Fig. 540-1). Upper urinary tract dilation is not diagnostic of obstruction and often persists after surgical correction of a significant obstructive lesion. Dilation can result from vesicoureteral reflux, or it may be a manifestation of abnormal development of the urinary tract, even when there is no obstruction. Renal length, degree of caliectasis and parenchymal thickness, and presence or absence of ureteral dilation should be assessed. Most pediatric urologists grade the severity of hydronephrosis from 1-4 using the Society for Fetal Urology grading scale (Table 540-4), whereas pediatric radiologists generally utilize the adjectives mild, moderate, and severe. The clinician should ascertain that the contralateral kidney is normal, and the bladder should be imaged to see whether the bladder wall is thickened, the lower ureter is dilated, and bladder emptying is complete. In acute or intermittent obstruction, the dilation of the collecting system may be minimal and ultrasonography may be misleading.

Voiding Cystourethrograph
In neonates and infants with congenital grade 3 or 4 hydronephrosis and in any child with ureteral dilation, a contrast voiding cystourethrograph (VCUG) should be obtained, because the dilation is secondary to vesicoureteral reflux in 15% of cases. In boys, the VCUG also is performed to rule out urethral obstruction, particularly in cases of suspected posterior urethral valves. In older children, the urinary flow rate can be measured noninvasively with a urinary flowmeter; decreased flow with a normal bladder contraction suggests infravesical obstruction (e.g., posterior urethral valves, urethral stricture). When the urethra cannot be catheterized to obtain a VCUG, the clinician should suspect a urethral stricture or an obstructive urethral lesion. Retrograde urethrography with contrast medium injected into the urethral meatus helps delineate the anatomy of the urethral obstruction.

Radioisotope Studies
Renal scintigraphy is used to assess renal anatomy and function. The 2 most commonly used radiopharmaceuticals are mercaptoacetyltriglycine (MAG-3) and technetium-99m-labeled dimercaptosuccinic acid. MAG-3, which is excreted by renal tubular secretion, is used to assess differential renal function, and when furosemide is administered, drainage also can be measured. An alternative to MAG-3 is diethylene tetracetic acid, which is cleared by glomerular filtration. The background activity of diethylene tetracetic acid is much higher than that of MAG-3. Dimercaptosuccinic acid is a renal cortical imaging agent and is used to assess differential renal function and to demonstrate whether renal scarring is present. It is used infrequently in children with obstructive uropathy.

In a MAG-3 diuretic renogram, a small dose of technetium-labeled MAG-3 is injected intravenously (Figs. 540-2 and 540-3). During the 1st 2-3 min, renal parenchymal uptake is analyzed and compared, allowing computation of differential renal function. Subsequently,
Magnetic Resonance Urography

MR urography is also used to evaluate suspected upper urinary tract pathology. The child is hydrated and given intravenous furosemide. Gadolinium-diethylene tetrapentaacetic acid is injected and routine T1-weighted and fat-suppressed fast spin-echo T2-weighted imaging is performed through the kidneys, ureters, and bladder. This study provides superb images of the pathology, and methodology permits assessment of differential renal function and drainage (Fig. 540-4). There is no radiation exposure; however, young children need sedation or anesthesia. It is used primarily when renal sonography and nuclear imaging fail to delineate complex pathology.

Computed Tomography

In children with a suspected ureteral calculus, noncontrast spiral CT of the abdomen and pelvis is a standard method of demonstrating whether a calculus is present, its location, and whether there is significant proximal hydronephrosis. This study is the initial study of choice in many of these patients. The disadvantage of CT is the significant radiation exposure, and it should be used only when the results will direct management decisions (see Chapter 718).

Ancillary Studies

In unusual cases, an antegrade pyelogram (insertion of a percutaneous nephrostomy tube and injection of contrast agent), can be performed to assess the anatomy of the upper urinary tract. This procedure usually requires general anesthesia. In addition, an antegrade pressure-perfusion flow study (Whitaker test) may be performed, in which fluid is infused at a measured rate, usually 10 mL/min. The pressures

Excretory Urogram

Excretory urogram is rarely used in assessing the pediatric urinary tract, although it may be useful in selected cases with indeterminate upper urinary tract obstruction or a suspected duplication anomaly.

Figure 540-2 Same patient as in Figure 540-1. MAG-3 diuretic renogram of a 6 wk old patient. The right kidney is on the right side of the image. A, Differential renal function: left kidney 70%, right kidney 30%. B, After administration of furosemide, drainage from the left kidney was normal and drainage from the right kidney was slow, consistent with right ureteropelvic junction obstruction. Pyeloplasty was performed on the right kidney.

Figure 540-3 Same patient as in Figure 540-1. A, MAG-3 diuretic renogram at 14 mo of age shows equal function in the 2 kidneys. B, Prompt drainage after the administration of furosemide.

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URETEROVESICAL OBSTRUCTION

In the renal pelvis and the bladder are monitored during this infusion, and pressure differences exceeding 20 cm H₂O suggest obstruction. In other cases, cystoscopy with retrograde pyelography provides excellent images of the upper urinary tract (Fig. 540-5).

SPECIFIC TYPES OF URINARY TRACT OBSTRUCTION AND THEIR TREATMENT

Hydrocalycosis

The term hydrocalycosis refers to a localized dilation of the calyx caused by obstruction of its infundibulum, termed infundibular stenosis. This condition can be developmental in origin or secondary to inflammatory processes, such as UTI. It usually is discovered during evaluation for pain or UTI. The diagnosis of infundibular stenosis is usually established by sonograph and CT scan or MR urography.

Ureteropelvic Junction Obstruction

UPJ obstruction is the most common obstructive lesion in childhood and usually is caused by intrinsic stenosis (see Figs. 540-1 to 540-3). An accessory artery to the lower pole of the kidney also can cause extrinsic obstruction. The typical appearance on ultrasonography is grade 3 or 4 hydronephrosis without a dilated ureter. UPJ obstruction most commonly manifests on antenatal sonography revealing fetal hydronephrosis; as a palpable renal mass in a newborn or infant; as abdominal, flank, or back pain; as a febrile UTI; or as hematuria after minimal trauma. Approximately 60% of cases occur on the left side, and the male:female ratio is 2:1. UPJ obstruction is bilateral in only 10% of cases. In kidneys with UPJ obstruction, renal function may be significantly impaired from pressure atrophy, but approximately half of affected kidneys have relatively normal glomerular function. The anomaly is corrected by performing a pyeloplasty, in which the stenotic segment is excised and the normal ureter and renal pelvis are reattached. Success rates are 91-98%. Pyeloplasty can be performed using laparoscopic techniques, often robotic-assisted using the da Vinci robot.

Lesser degrees of UPJ narrowing might cause mild hydronephrosis, which usually is nonobstructive, and typically these kidneys function normally. The spectrum of UPJ abnormalities has been referred to as anomalous UPJ. Another cause of mild hydronephrosis is fetal folds of the upper ureter, which also are nonobstructive.

The diagnosis can be difficult to establish in an asymptomatic infant in whom dilation of the renal pelvis is found incidentally in a prenatal ultrasonogram. After birth, the sonographic study is repeated to confirm the prenatal finding. A VCUG is necessary because 10-15% of patients have ipsilateral vesicoureteral reflex. Because neonatal oliguria can cause temporary decompression of a diluted renal pelvis, it is ideal to perform the first postnatal sonogram after the 3rd day of life. Delaying the sonogram may be impractical. If no dilation is found on the initial sonogram, a repeat study should be performed at 1 mo of age. If the kidney shows grade 1 or 2 hydronephrosis and the renal parenchyma appears normal, a period of observation usually is appropriate, with sequential renal ultrasonograms to monitor the severity of hydronephrosis, and the hydronephrosis usually disappears. Antibiotic prophylaxis is not indicated for children with mild hydronephrosis. If the hydronephrosis is grade 3 or 4, spontaneous resolution is less likely and obstruction is more likely to be present, particularly if the renal pelvic diameter is 3 cm. A diuretic renogram with MAG-3 is performed at 4-6 wk of age. If there is poor upper tract drainage or the differential renal function is poor, pyeloplasty is recommended. After pyeloplasty the differential renal function often improves, and improved drainage with furosemide stimulation is expected.

If the differential function on renography is normal, and drainage is satisfactory, the infant can be followed with serial ultrasonograms, even with grade 4 hydronephrosis. If the hydronephrosis remains severe with no improvement, a repeat diuretic renogram after 6-12 mo can help in the decision between continued observation and surgical repair. Prompt surgical repair is indicated in infants with an abdominal mass, bilateral severe hydronephrosis, a solitary kidney, or diminished function in the involved kidney. In unusual cases in which the differential renal function is <10% but the kidney definitely has some function, insertion of a percutaneous nephrostomy tube allows drainage of the hydronephrotic kidney for a few weeks to allow reassessment of renal function. In older children who present with symptoms, the diagnosis of UPJ obstruction usually is established by ultrasonography and diuretic renography.
The following entities should be considered in the differential diagnosis: megacalycosis, a congenital nonobstructive dilation of the calyces without pelvic or ureteric dilation; vesicoureteral reflux with marked dilation and kinking of the ureter; midureteral or distal ureteral obstruction when the ureter is not well visualized on the urogram; and retrocaval ureter.

**Midureteral Obstruction**
Congenital ureteral stenosis or a ureteral valve in the midureter is rare. It is corrected by excision of the strictured segment and reanastomosis of the normal upper and lower ureteral segments. A retrocaval ureter is an anomaly in which the upper right ureter travels posterior to the inferior vena cava. In this anomaly, the vena cava can cause extrinsic compression and obstruction. An IVP or MR urogram shows the right ureter to be medially deviated at the level of the 3rd lumbar vertebra. The diagnosis may be confirmed by retrograde pyelography (see Fig. 540-5). Surgical treatment consists of transection of the upper ureter, moving it anterior to the vena cava, and reanastomosing the upper and lower segments. Repair is necessary only when obstruction is present. Retroperitoneal tumors, fibrosis caused by surgical procedures, inflammatory processes (as in chronic granulomatous disease), and radiation therapy can cause acquired midureteral obstruction.

**Ureterocele**
A ureterocele is a cystic dilation of the terminal ureter and is obstructive because of a pinpoint ureteral orifice. Ureteroceles are much more common in girls than in boys. Affected children usually are discovered by prenatal ultrasonography, but some present with a febrile UTI. Ureteroceles may be ectopic, in which case the cystic swelling extends through the bladder neck into the urethra, or orthotopic, in which case the ureterocele is entirely within the bladder. Both orthotopic and ectopic ureteroceles can be bilateral.

In girls, ureteroceles nearly always are associated with ureteral duplication (Fig. 540-7), whereas in 50% of affected boys there is only 1 ureter.

**Ectopic Ureter**
A ureter that drains outside the bladder is referred to as an ectopic ureter. This anomaly is 3 times as common in girls as in boys and usually is detected prenatally. The ectopic ureter typically drains the upper pole of a duplex collecting system (2 ureters).

In girls, approximately 35% of these ureters enter the urethra at the bladder neck, 35% enter the urethrovaginal septum, 25% enter the vagina, and a few drain into the cervix, uterus, Gartner duct, or a urethral diverticulum. Often the terminal aspect of the ureter is narrowed, causing hydronephrosis. With the exception of the ectopic ureter entering the bladder neck, in girls an ectopic ureter causes continuous urinary incontinence from the affected renal moiety. UTI is common because of urinary stasis.

In boys, ectopic ureters enter the posterior urethra (above the external sphincter) in 47%, the prostatic urethre in 10%, the seminal vesicle in 33%, the ejaculatory duct in 5%, and the vas deferens in 5%. Consequently, in boys, an ectopic ureter does not cause incontinence, and most patients present with a UTI or epididymitis.

Evaluation includes a renal sonogram, VCUG, and renal scan, which demonstrates whether the affected segment has significant function. The sonogram shows the affected hydronephrotic kidney or dilated upper pole and ureter down to the bladder (Fig. 540-6). If the ectopic ureter drains into the bladder neck (female), a VCUG usually shows reflux into the ureter. Otherwise, there is no reflux into the ectopic ureter, but there may be reflux into the ipsilateral lower pole ureter or contralateral collecting system.

**Treatment** depends on the status of the renal unit drained by the ectopic ureter. If there is satisfactory function, ureteral reimplantation into the bladder or ureteroureterostomy (anastomosing the ectopic upper pole ureter into the normally inserting lower pole ureter) is indicated. If function is poor, partial or total nephrectomy is indicated. In many centers this procedure is done laparoscopically and often with robotic assistance using the da Vinci robot.

**Figure 540-6** Ultrasonographic image of the right dilated ureter (bottom arrows) extending behind and caudal to a nearly empty bladder (top arrow) in a girl with urinary incontinence and ectopic ureter draining into the vagina.

**Figure 540-7** A, Infant with ectopic ureterocele. Sonogram of the left kidney shows massive dilation of the upper pole and a normal lower pole. B, Voiding cystourethrogram shows large ureterocele, draining the left upper pole, in the bladder. No reflux is present.
ureters. In most nonobstructed megaureters, the hydroureteronephrosis suggests obstruction. Macroscopic examination of the kidney may show malrotation or thinning of the renal parenchyma. Ultrasonography is sensitive for detecting the ureterocele in the bladder and hydroureteronephrosis. IVP reveals varying degrees of ureteral and calyceal dilation, and there is a round filling defect in the bladder. In delayed films, cystic dilation of the ureter may be clearly visible and full of contrast material. Transurethral incision of the ureterocele effectively relieves the obstruction, but it can result in vesicoureteral reflux, necessitating ureteral reimplantation later. Some prefer open excision of the ureterocele and reimplantation as the initial form of treatment. Simple ureteroceles discovered incidentally without upper tract dilation generally do not require treatment.

Orthotopic ureteroceles are associated with duplicated or single collecting systems, and the orifice is in the expected location in the bladder (Fig. 540-8). These anomalies usually are discovered during an investigation for prenatal hydronephrosis or a UTI. Ultrasonography is sensitive for detecting the ureterocele in the bladder and hydroureteronephrosis. IVP reveals varying degrees of ureteral and calyceal dilation, and there is a round filling defect in the bladder. In delayed films, cystic dilation of the ureter may be clearly visible and full of contrast material. Transurethral incision of the ureterocele effectively relieves the obstruction, but it can result in vesicoureteral reflux, necessitating ureteral reimplantation later. Some prefer open excision of the ureterocele and reimplantation as the initial form of treatment. Small, simple ureteroceles discovered incidentally without upper tract dilation generally do not require treatment.

Megaureter

Table 540-5 presents a classification of megaureters (dilated ureter). Numerous disorders can cause ureteral dilation, and many are nonobstructive.

Megaureters usually are discovered during prenatal sonography, postnatal UTI, hematuria, or abdominal pain. A careful history, physical examination, and VCUG identify causes of secondary megaureters and refluxing megaureters as well as the prune-belly syndrome. Primary obstructed megaureters and nonobstructed megaureters probably represent varying degrees of severity of the same anomaly.

The primary obstructed nonrefluxing megaureter results from abnormal development of the distal ureter, with collagenous tissue replacing the muscle layer. Normal ureteral peristalsis is disrupted, and the proximal ureter widens. In most cases there is not a true stricture. On IVP or an MR urogram, the distal ureter is more dilated in its distal segment and tapers abruptly at or above the junction of the bladder (Fig. 540-9). The lesion may be unilateral or bilateral. Significant hydroureteronephrosis suggests obstruction. Megaureter predisposes to UTI, urinary stones, hematuria, and flank pain because of urinary stasis. In most cases, diuretic renography and sequential sonographic studies can reliably differentiate obstructed from nonobstructed megaureters. In most nonobstructed megaureters, the hydroureteronephrosis diminishes gradually (Fig. 540-10). Truly obstructed megaureters require surgical treatment, with excision of the narrowed segment, ureteral tapering, and reimplantation of the ureter. The results of surgical reconstruction usually are good, but the prognosis depends on preexisting renal function and whether complications develop.

If differential renal function is normal (>45%) and the child is asymptomatic, it is safe to manage the patient with observation with serial ultrasonography and periodic diuretic renography to monitor renal function and drainage. In children with grade 4 hydroureteronephrosis, prophylactic antimicrobial therapy should be prescribed, as these children are prone to upper UTI. If renal function deteriorates, upper urinary tract drainage slows, or UTI occurs, ureteral reimplantation is recommended. Approximately 15% of children with a nonrefluxing megaureter undergo ureteral reimplantation.

Prune-Belly Syndrome

Prune-belly syndrome, also called triad syndrome or Eagle-Barrett syndrome, occurs in approximately 1 in 40,000 births; 95% of affected children are male. The characteristic association of deficient abdominal muscles, undescended testes, and urinary tract abnormalities probably results from severe urethral obstruction in fetal life (Fig. 540-11). Oligohydramnios and pulmonary hypoplasia are common complications in the perinatal period. Many affected infants are stillborn. Urinary tract abnormalities include massive dilation of the ureters and upper tracts and a very large bladder, with a patent urachus or a urachal diverticulum. Most patients have vesicoureteral reflux. The prostatic urethra usually is dilated, and the prostate is hypoplastic. The anterior urethra may be dilated, resulting in a megalourethra. Rarely, there is urethral stenosis or atresia. The kidneys usually show various degrees of dysplasia, and the testes usually are intraabdominal. Malrotation of the bowel often is present. Cardiac abnormalities occur in 10% of cases; >50% have abnormalities of the musculoskeletal system, including
Obstructed Classification of Megaureter

Table 540-5  Classification of Megaureter

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<td>Ectopic uterocele</td>
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<td></td>
<td>Nonrefluxing, nonobstructive</td>
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<td>Diabetes insipidus</td>
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Figure 540-9  Obstructed nonrefluxing megaureter. Excretory urogram in a girl with a history of a febrile urinary tract infection. The right side is normal. The left side reveals hydroureronephrosis with predominant dilation of the distal ureter. Note the characteristic appearance of the distal ureter. There was no vesicoureteral reflux. The diagnosis of obstruction was confirmed by diuretic renography.

limb abnormalities and scoliosis. In girls, anomalies of the urethra, uterus, and vagina usually are present.

Many neonates with prune-belly syndrome have difficulty with effective bladder emptying because the bladder musculature is poorly developed, and the urethra may be narrowed. When no obstruction is present, the goal of treatment is the prevention of UTI with antibiotic prophylaxis. When obstruction of the ureters or urethra is demonstrated, temporary drainage procedures, such as a vesicostomy, can help to preserve renal function until the child is old enough for surgery. Some children with prune-belly syndrome have been found to have classic or atypical posterior urethral valves. UTIs occur often and should be treated promptly. Correction of the undescended testes by orchiopexy can be difficult in these children because the testes are located high in the abdomen and surgery is best accomplished in the 1st 6 mo of life. Reconstruction of the abdominal wall offers cosmetic and functional benefits.

The prognosis ultimately depends on the degree of pulmonary hypoplasia and renal dysplasia. One third of children with prune-belly syndrome are stillborn or die in the 1st few mo of life because of pulmonary hypoplasia. As many as 30% of the long-term survivors develop end-stage renal disease from dysplasia or complications of infection or reflux and eventually require renal transplantation. Renal transplantation in these children offers good results.

Bladder Neck Obstruction

Bladder neck obstruction usually is secondary to ectopic ureterocele, bladder calculi, or a tumor of the prostate (rhabdomyosarcoma). The manifestations include difficulty voiding, urinary retention, UTI, and bladder distention with overflow incontinence. Apparent bladder neck obstruction is common in cases of posterior urethral valves, but it seldom has any functional significance. Primary bladder neck obstruction is extremely rare.

Posterior Urethral Valves

The most common cause of severe obstructive uropathy in children is posterior urethral valves, affecting 1 in 8,000 boys. The urethral valves are tissue leaflets fanning distally from the prostatic urethra to the external urinary sphincter. A slit-like opening usually separates the leaflets. Valves are of unclear embryologic origin and cause varying degrees of obstruction. Approximately 30% of patients experience end-stage renal disease or chronic renal insufficiency. The prostatic urethra dilates, and the bladder muscle undergoes hypertrophy. Vesicoureteral reflux occurs in 50% of patients, and distal ureteral obstruction can result from a chronically distended bladder or bladder muscle hyper trophy. The renal changes range from mild hydronephrosis to severe renal dysplasia; their severity probably depends on the severity of the obstruction and its time of onset during fetal development. As in other cases of obstruction or renal dysplasia, there may be oligohydramnios and pulmonary hypoplasia.

Affected boys with posterior urethral valves often are discovered prenatally when maternal ultrasonography reveals bilateral hydronephrosis, a distended bladder, and the obstruction is severe, oligohydramnios. Prenatal bladder decompression by percutaneous vesicoamniotic shunt or open fetal surgery has been reported. Experimental and clinical evidence of the possible benefits of fetal intervention is lacking, and few affected fetuses are candidates. Prenatally diagnosed posterior urethral valves, particularly when discovered in the 2nd trimester, carry a poorer prognosis than those detected in the 3rd trimester following a normal second fetal ultrasound. In the male neonate, posterior urethral valves are suspected when there is a palpably distended bladder and the urinary stream is weak. If the obstruction is severe and goes unrecognized during the neonatal period, infants can present later in life with failure to thrive because of uremia or sepsis caused by infection in the obstructed urinary tract. With lesser degrees of obstruction, children present later in life with difficulty in achieving diurnal urinary continence or with UTI. The diagnosis is established with a VCUG (Fig. 540-12) or by perineal ultrasonography.

After the diagnosis is established, renal function and the anatomy of the upper urinary tract should be carefully evaluated. In the healthy neonate, a small polyethylene feeding tube (No. 5 or No. 8 French) is inserted in the bladder and left for several days. Passing the feeding
Favorable prognostic factors include a normal prenatal ultrasonogram between 18 and 24 wk of gestation, a serum creatinine level <0.8-1.0 mg/dL after bladder decompression, and visualization of the corticomedullary junction on renal sonography. In several situations, a “popoff valve” can occur during urinary tract development, which preserves the integrity of 1 or both kidneys. For example, 15% of boys with posterior urethral valves have unilateral reflux into a nonfunctioning dysplastic kidney, termed the VURD syndrome (valves, unilateral reflux, dysplasia). In these boys, the high bladder pressure is dissipated into the nonfunctioning kidney, allowing normal development of the contralateral kidney.

If the serum creatinine level remains high or increases despite bladder drainage by a small catheter, secondary ureteral obstruction, irreversible renal damage, or renal dysplasia should be suspected. In such cases, a vescostomy should be considered. Cutaneous pyelostomy rarely affords better drainage when compared with cutaneous vesicostomy, and the latter also allows continued bladder growth and gradual improvement in bladder wall compliance.

In the septic and uremic infant, lifesaving measures must include prompt correction of the electrolyte imbalance and control of the infection by appropriate antibiotics. Drainage of the upper tracts by percutaneous nephrostomy and hemodialysis may be necessary. If the patient’s condition becomes stable, evaluation and treatment may be undertaken. Posterior valves are diagnosed in some older boys because of a poor stream, diurnal incontinence, or a UTI; these boys generally are treated by primary valve ablation.

Favorable prognostic factors include a normal prenatal ultrasonogram between 18 and 24 wk of gestation, a serum creatinine level <0.8-1.0 mg/dL after bladder decompression, and visualization of the corticomedullary junction on renal sonography. In several situations, a “popoff valve” can occur during urinary tract development, which preserves the integrity of 1 or both kidneys. For example, 15% of boys with posterior urethral valves have unilateral reflux into a nonfunctioning dysplastic kidney, termed the VURD syndrome (valves, unilateral reflux, dysplasia). In these boys, the high bladder pressure is dissipated into the nonfunctioning kidney, allowing normal development of the contralateral kidney. In newborn boys with urinary ascites, the urine generally leaks out from the obstructed collecting system through the renal fornices, allowing normal development of the kidneys. Unfavorable prognostic factors include the presence of oligohydramnios in utero, identification of hydronephrosis before 24 wk of gestation, a serum creatinine level >1.0 mg/dL after bladder decompression, identification of cortical cysts in both kidneys, and persistence of diurnal incontinence beyond 5 yr of age.
commonly, the obstruction causes symptoms of bladder instability, the urinary stream is seldom noticed by the child or the parents. More because these lesions can develop gradually, the decrease in force of dilation, or continent urinary diversion.

Treatment includes urethral reconstruction, gradual urethral is variable. The most severely affected boys have end-stage renal surgery. If there is any significant degree of renal dysfunction, renal function. Urinary incontinence usually improves with age, par particularly after puberty. Meticulous attention to bladder compliance, emptied, and infection can improve results in the future.

Urethral Atresia
The most severe form of obstructive uropathy in boys is urethral atresia, a rare condition. In utero there is a distended bladder, bilateral hydrourteronephrosis, and oligohydramnios. In most cases, these infants are stillborn or succumb to pulmonary hypoplasia. Some boys with prune-belly syndrome also have urethral atresia. If the urachus is patent, oligohydramnios is unlikely and the infant usually survives. Urethral reconstruction is difficult, and most patients are managed with continent urinary diversion.

Urethral Hypoplasia
Urethral hypoplasia is a rare form of obstructive uropathy in boys that is less severe than urethral atresia. In urethral hypoplasia, the urethral lumen is extremely small. Neonates with urethral hypoplasia typically have bilateral hydrouretonephrosis and a distended bladder. Passage of a small pediatric feeding tube through the urethra is difficult or impossible. Usually a cutaneous vesicostomy must be performed to relieve upper urinary tract obstruction, and the severity of renal insufficiency is variable. The most severely affected boys have end-stage renal disease. Treatment includes urethral reconstruction, gradual urethral dilation, or continent urinary diversion.

Urethral Strictures
Urethral strictures in boys usually result from urethral trauma, either iatrogenic (catheterization, endoscopic procedures, previous urethral reconstruction) or accidental (straddle injuries, pelvic fractures). Because these lesions can develop gradually, the decrease in force of the urinary stream is seldom noticed by the child or the parents. More commonly, the obstruction causes symptoms of bladder instability, hematuria, or dysuria. Catheterization of the bladder usually is impossible. The diagnosis is made by a retrograde urethrogram, in which contrast is injected toward the bladder through a catheter inserted into the distal urethra. Ultrasonography also has been used to diagnose urethral strictures. Endoscopy is confirmatory. Endoscopic treatment of short strictures by direct vision urethrotomy is often successful initially and results in a profoundly improved urinary stream, but often the stricture recurs and is found at long-term follow-up. Longer strictures surrounded by periurethral fibrosis often require urethroplasty. Repeated endoscopic procedures generally should be avoided, because they can cause additional urethral damage. Noninvasive measurement of the urinary flow rate and pattern is useful for diagnosis and follow-up.

In girls, true urethral strictures are rare because the female urethra is protected from trauma, particularly in childhood. In the past it was thought that a distal urethral ring commonly caused obstruction of the female urethra and UTI and that affected girls benefited from urethral dilation. The diagnosis was suspected when a “spinning top” deformity of the urethra was found in the VCUG (see Fig. 543-3 in Chapter 543) and was confirmed by urethral calibration. There is no correlation between the radiologic appearance of the urethra in the VCUG and the urethral caliber and no significant difference in urethral caliber between girls with recurrent cystitis and normal age-matched controls. The finding usually is secondary to detrusor–sphincter dyssynergia. Consequently, urethral dilation in girls rarely is indicated.

Anterior Urethral Valves and Urethral Diverticula in the Male
Anterior urethral valves are rare. The obstruction is not obstructing valve leaflets, as occurs in the posterior urethra. Rather, it is a urethral diverticulum in the penile urethra that expands during voiding. Distal extension of the diverticulum causes extrinsic compression of the distal penile urethra, causing urethral obstruction. Typically there is a soft mass on the ventral surface of the penis at the penoscrotal junction. In addition, the urinary stream often is weak, and the physical findings associated with posterior urethral valves often are present. The diverticulum may be small and minimally obstructive, or, in other cases, may be severely obstructive and cause renal insufficiency. The diagnosis is suspected on physical examination and is confirmed by the VCUG. Treatment involves open excision of the diverticulum or transurethral excision of the distal urethral cusp. Urethral diverticula occasionally occur after extensive hypospadias repair. Fusiform dilation of the urethra or megalourethra can result from underdevelopment of the corpus spongiosum and support structures of the urethra. This condition is commonly associated with the prune-belly syndrome.

Male Urethral Meatal Stenosis
See Chapter 544 for information on urethral meatal stenosis in males.

Bibliography is available at Expert Consult.
Bibliography


BLADDER EXSTROPHY

Exstrophy of the urinary bladder occurs in approximately 1 in 35,000-40,000 births. The male:female ratio is 2:1. The severity ranges from simple epispadias (in boys) to complete exstrophy of the cloaca involving exposure of the entire hindgut and the bladder (termed cloacal exstrophy).
Part XXIV ♦ Urologic Disorders in Infants and Children

Clinical Manifestations
Anomalies of the bladder are hypothesized to result when the mesoderm fails to invade the cephalad extension of the cloacal membrane; the extent of this failure determines the degree of the anomaly. In classic bladder extrophy (Fig. 541-1), the bladder protrudes from the abdominal wall and its mucosa is exposed. The umbilicus is displaced downward, the pubic rami are widely separated in the midline, and the rectus muscles are separated. In boys, there is complete epispadias with dorsal chordee, and the overall penile length is approximately half that of unaffected boys. The scrotum typically is separated slightly from the penis and is wide and shallow. Undescended testes and inguinal hernias are common. Girls also have epispadias, with separation of the 2 halves of the clitoris and wide separation of the labia. The anus is displaced anteriorly in both sexes, and there may be rectal prolapse. The pubic rami are widely separated. Persons with extrophy tend to be shorter than normal.

The consequences of untreated bladder extrophy are total urinary incontinence and an increased incidence of bladder cancer, usually adenocarcinoma. The genital deformities can produce sexual disability in both sexes, particularly in males. The wide separation of the pubic rami causes a characteristic broad-based gait but no significant disability. In classic bladder extrophy, the upper urinary tracts usually are normal.

Treatment
Management of bladder extrophy should start at birth. The bladder should be covered with plastic wrap to keep the bladder mucosa moist. Application of gauze or petroleum-gauze to the bladder mucosa should be avoided, because significant inflammation will result. The infant should be transferred promptly to a center with pediatric urologic and anesthetic support for the treatment of such anomalies. These children are prone to latex allergy, so latex precautions should be practiced in their care.

There are 2 surgical approaches: staged reconstruction and total single-stage reconstruction. Most babies also undergo bilateral iliac osteotomy, which allows the pubic symphysis to be approximated, which supports the bladder closure. In a staged reconstruction, the initial stage is bladder closure, the 2nd stage (in boys) is epispadias repair, and the final stage is bladder neck reconstruction. The single-stage reconstruction attempts to reconstruct the entire malformation in a single procedure. When this operation is performed in the newborn, there is an increased risk of intraoperative penile injury and postoperative hydroureteronephrosis, compared with the staged reconstruction. The complication rate is high with both approaches and there is no consensus on which is better.

Although bladder closure within 48 hr has been the standard in the past, more recently, many centers of excellence defer the procedure for 1-2 wk to be certain that the appropriate experienced surgical and anesthetic team is available. During bladder extrophy closure, the abdominal wall is mobilized and the pubic rami are brought together in the midline following pelvic osteotomy. Early bladder closure can be performed in almost all neonates with classic bladder extrophy. Treatment should be deferred in selected situations when surgical therapy would be excessively risky or complex, such as in a premature baby or when it would have to be performed by inexperienced surgeons. In the staged approach, in boys, epispadias repair usually is performed at 1-2 yr of age. At this point the child has total urinary incontinence because there is no functional external urinary sphincter. At 3-6 yr, if the bladder is sufficiently large, bladder neck reconstruction is performed to try to create a functional sphincter.

Total single-stage reconstruction includes closure of the bladder, closure of the abdominal wall, and, in boys, correction of epispadias using a technique of penile disassembly, in which the 2 corpora cavernosa and the midline urethra are mobilized separately into 3 parts. Postoperatively, the infant’s upper urinary tract is monitored closely for the possible development of hydronephrosis and infection. Most infants with bladder extrophy have vesicoureteral reflux and should receive antibiotic prophylaxis. The final stage of reconstruction involves creation of a sphincter muscle for bladder control and correction of the vesicoureteral reflux. At this point the child is 3-6 yr old, the bladder capacity should be at least 80-90 mL, and the child must have gained rectal control. Typically, bladder capacity is monitored every 12-24 mo using cystoscopy under anesthesia.

At puberty, often the pubic hair is distributed to the sides of the external genitals. A monoplasty can be performed to provide a normal escutcheon.

Long-Term Prognosis
This plan of treatment has yielded a continence rate of 60-70% in a few centers, with <15% deterioration of the upper urinary tract. This continence rate reflects not only the successful reconstruction but also the quality and size of the bladder. The reconstructed bladder neck does not relax during voiding as in a normal child; instead the patient must void byValsalva. Children who undergo reconstructive surgery as newborns have a greater chance of obtaining a normally functioning bladder.

Children who remain incontinent for more than 1 yr after bladder neck reconstruction or those who are not eligible for bladder neck reconstruction because of a small bladder capacity are candidates for an alternative reconstructive procedure to achieve dryness. In selected cases, cystoscopic injection of dextranomer or polymethylsiloxane microspheres into the bladder neck can provide sufficient bladder neck coaptation to establish continence. Alternatively, if the child is not a candidate for endoscopic therapy, options include:

- Augmentation cystoplasty, in which the bladder is enlarged with a patch of small or large bowel to increase its capacity.
- Creation of a neobladder out of small and large bowel with placement of a continent abdominal stoma through which clean intermittent catheterization can be performed.
- Placement of an artificial urinary sphincter, with possible augmentation cystoplasty.
- Ureterosigmoidostomy, in which the ureters are detached from the bladder and sutured to the sigmoid colon; individuals void urine and stool from the rectum and rely on their anal sphincter for continence.
- Mainz II procedure, in which the sigmoid colon is reconfigured into a “bladder” into which the ureters are connected, and the patient voids 3-6 times daily through the rectum, and the stool tends to be more solid.

Ureterosigmoidostomy carries a significant risk of chronic pyelonephritis (see Chapter 538), upper urinary tract damage, metabolic acidosis resulting from absorption of hydrogen ion and chloride in the intestine, and at least a 15% long-term risk of colon carcinoma. Patients from less-developed countries often undergo the Mainz II procedure because the continence rate is high and pyelonephritis and upper tract changes are uncommon.
Late follow-up has shown that although men with exstrophy have a penis that is half normal length, they usually experience satisfactory sexual function. Fertility has been low, possibly because of iatrogenic injury to the secondary sexual organs during reconstruction. With artificial reproductive technology, nearly all men can be fertile. In women, fertility is not affected, but uterine prolapse during pregnancy is a problem. In women who have undergone a continent urinary diversion, delivery by cesarean section may be necessary.

OTHER EXSTROPHY ANOMALIES

Children with more complex cases of cloacal exstrophy, which has an incidence of 1 in 400,000, have an omphalocele and severe abnormalities of the colon and the rectum and often have short bowel syndrome (see Chapter 338.7), the most devastating anomaly managed by pediatric urologists. Approximately 50% of patients have an upper urinary tract anomaly, and 50% have spina bifida (see Chapter 591). Children with cloacal exstrophy do not achieve normal urine or stool continence. Reconstructive techniques result in a satisfactory outcome in most patients with permanent urinary diversion (either ileal conduit or continent urinary diversion) and a colostomy. Because the penis in boys with cloacal exstrophy usually is diminutive, genital reconstruction in boys with cloacal exstrophy has been unsatisfactory. Until recently, most specialists recommended assigning a female gender to such infants, but currently there is debate whether these children, who have a 46,XY karyotype and androgen imprinting in utero, can have a satisfactory female gender identity (see Chapter 110.2). Many assume male gender characteristics by adolescence. Decisions regarding gender assignment should be made jointly by the physicians caring for the infant (surgical team, pediatric endocrinologist, child psychiatrist, and ethicist) and family.

Epispadias is in the spectrum of exstrophy anomalies, affecting approximately 1 in 117,000 boys and 1 in 480,000 girls. In boys, the diagnosis is obvious because the prepuce is distributed primarily on the ventral aspect of the penis shaft and the urethral meatus is on the dorsum of the penis. Distal epispadias in boys usually is associated with normal urinary control and normal upper urinary tracts and should be repaired by 6-12 mo of age. In girls, the clitoris is bifid and the urethra is split dorsally (Fig. 541-2). In more severely affected boys and in all girls with epispadias, there is total urinary incontinence because the sphincter is incompletely formed, and there is wide separation of the pubic rami. These children require surgical reconstruction of the bladder neck, similar to the final management stage in children with classic bladder exstrophy.

BLADDER DIVERTICULA

Bladder diverticula develop as herniations of bladder mucosa between defects of bladder smooth muscle fibers. Primary bladder diverticula usually develop at the ureterovesical junction and may be associated with vesicoureteral reflux, because the diverticulum interferes with the normal flap-valve attachment between the ureter and bladder. In rare circumstances the diverticulum is so large that it interferes with normal micturition by obstructing the bladder neck. Bladder diverticula also commonly are associated with distal urethral obstruction such as posterior urethral valves or neurogenic bladder dysfunction. They occur commonly in children with connective tissue disorders including Williams syndrome, Ehlers-Danlos syndrome, and Menkes syndrome (Fig. 541-3). Small diverticula require no treatment other than that of the primary disease, whereas large diverticula can contribute to inefficient voiding, residual urine, urinary stasis, and urinary tract infections and should be excised.

URACHAL ANOMALIES

The urachus is an embryologic canal connecting the dome of the fetal bladder with the allantois, a structure that contributes to the formation of the umbilical cord. The lumen of the urachus is normally obliterated during embryonic development, transforming the urachus into a solid cord. Urachal abnormalities are more common in boys than in girls. A patent urachus can occur as an isolated anomaly; it may be associated with prune-belly syndrome or posterior urethral valves (see Chapter 540). In this condition there is continuous urinary drainage from the umbilicus. The tract should be excised. Another urachal anomaly is the urachal cyst, which can become infected. Typical symptoms and physical findings include suprapubic pain, fever, irritative voiding symptoms, and an infraumbilical mass, which can be erythematous. Diagnosis is made by ultrasonography or CT (Fig. 541-4).
Treatment is intravenous antibiotic therapy and drainage and excision. Other urachal anomalies include the vesicourachal diverticulum, which is a diverticulum of the bladder dome, and umbilical–urachal sinus, which is a blind external sinus that opens at the umbilicus. These lesions should be excised.

*Bibliography is available at Expert Consult.*
Bibliography


Neuropathic bladder dysfunction in children usually is congenital, generally resulting from neural tube defects or other spinal abnormalities. Acquired diseases and traumatic lesions of the spinal cord are less common. Central nervous system tumors, sacrococcygeal teratoma, spinal abnormalities associated with imperforate anus (see Chapter 344), and spinal cord trauma also can result in abnormal innervation of the bladder and/or sphincter.

NEURAL TUBE DEFECTS

Neural tube defects, resulting from failure of the neural tube to close spontaneously between the 3rd and 4th wk in utero, result in abnormalities of the vertebral column that affect spinal cord function, including myelomeningocele and meningomyelocele. A few medical centers in the United States have been performing antenatal myelomeningocele closure. Long-term results from one large trial (the "MOMS trial"), have not shown a definite improvement in lower urinary tract function, although some children have demonstrated nearly normal bladder function, and overall there has been a significant reduction in the need for ventriculoperitoneal shunting.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most important urologic consequences of neuropathic bladder dysfunction associated with neural tube defects are urinary incontinence (see Chapter 543), urinary tract infections (UTIs; see Chapter 538), and hydronephrosis from vesicoureteral reflux (see Chapter 539), or detrusor–sphincter dyssynergia (see Chapter 540). Pyelonephritis and renal functional deterioration (see Chapter 535) are common causes of premature death of affected patients. In the neonate, renal ultrasonography, assessment of postvoid residual urine volumes, and a voiding cystourethrogram are performed after closure of the myelomeningocele. Approximately 10-15% of newborns with myelomeningocele have hydronephrosis, and renal malformations are common; 25% have vesicoureteral reflux. A urodynamic study also should be performed. This study involves filling the bladder with saline, measuring the bladder volume and pressure, and assessing sphincter tone. During bladder filling, the bladder might show (1) uninhibited (premature) contractions (termed hyperreflexia) at low volumes, (2) normal bladder volume with contraction at an appropriate volume, or (3) atonia (lack of bladder contraction). Bladder compliance or elasticity also may be reduced. The sphincter can show (1) normal tone with relaxation during bladder contraction, (2) reduced or absent tone, or (3) normal or increased tone that increases during a bladder contraction (termed detrusor-sphincter dyssynergia) (Fig. 542-1). The most important urologic consequences of neuropathic bladder dysfunction associated with neural tube defects are urinary incontinence (see Chapter 543), urinary tract infections (UTIs; see Chapter 538), and hydronephrosis from vesicoureteral reflux (see Chapter 539), or detrusor–sphincter dyssynergia (see Chapter 540). Pyelonephritis and renal functional deterioration (see Chapter 535) are common causes of premature death of affected patients. In the neonate, renal ultrasonography, assessment of postvoid residual urine volumes, and a voiding cystourethrogram are performed after closure of the myelomeningocele. Approximately 10-15% of newborns with myelomeningocele have hydronephrosis, and renal malformations are common; 25% have vesicoureteral reflux. A urodynamic study also should be performed. This study involves filling the bladder with saline, measuring the bladder volume and pressure, and assessing sphincter tone. During bladder filling, the bladder might show (1) uninhibited (premature) contractions (termed hyperreflexia) at low volumes, (2) normal bladder volume with contraction at an appropriate volume, or (3) atonia (lack of bladder contraction). Bladder compliance or elasticity also may be reduced. The sphincter can show (1) normal tone with relaxation during bladder contraction, (2) reduced or absent tone, or (3) normal or increased tone that increases during a bladder contraction (termed detrusor-sphincter dyssynergia) (Fig. 542-1).
URINARY INCONTINENCE

Incontinence in the child with neuropathic bladder can result from total or partial denervation of the sphincter, bladder hyperreflexia, poor bladder compliance, chronic urinary retention, or a combination of these factors.

Incontinence often is addressed around 4 yr of age and is tailored to the individual child. Nearly all children require clean intermittent catheterization to stay dry. This technique allows efficient bladder emptying with minimal risk of symptomatic UTI. The urinary tract should be reevaluated with renal ultrasonography, a voiding cystourethrogram, and a urodynamic study, including bladder capacity. If the external sphincter tone is sufficient and the bladder has adequate compliance, intermittent catheterization every 3-4 hr usually is successful in keeping the child dry. If there are unstable bladder contractions, an anticholinergic medication such as oxybutynin chloride, hyoscyamine, or tolterodine is prescribed to increase bladder capacity. If there is sphincter incompetence, α-adrenergic medications are prescribed to enhance outlet resistance. Bacteriuria is seen in up to 50% of children using intermittent self-catheterization, but it seldom causes symptoms. In the absence of reflux, there seems to be little cause for concern. Performing intermittent catheterization with a new catheter (hydrophilic or standard silicone) each time also is quite effective in preventing bacteriuria and avoids the need for antibiotic prophylaxis. With this treatment plan, 40-85% of patients are dry, depending on the definition of continence; some children wear a pad in their underwear or a diaper but feel that they are dry.

If there is persistent incontinence despite medical therapy, reconstructive urinary tract surgery nearly always can provide complete or satisfactory continence. If urethral resistance is low, bladder neck reconstructive procedures such as a periurethral sling often are successful. Alternatively, implantation of an artificial sphincter usually is successful. This sphincter consists of an inflatable cuff that is placed around the bladder neck, a pressure-regulating balloon implanted in the extraperitoneal space, and a pumping mechanism that is implanted in the scrotum of boys and in the labia majora of girls. If the bladder capacity or bladder compliance is low, or if there are persistent uninhibited contractions despite anticholinergic therapy, enlargement of the bladder with a patch of small or large intestine, termed augmentation cystoplasty or enteroctystoplasty, is effective.

These patients still need to perform clean intermittent catheterization. If urethral catheterization is difficult, a continent urinary stoma may be incorporated into the urinary tract reconstruction. A common method is the Mitrofanoff procedure, in which the appendix is isolated from the cecum on its vascular pedicle and is interposed between the bladder and abdominal wall to allow intermittent catheterization through a dry stoma. An ileal conduit with a bag on the abdominal wall is rarely used.

Complications of Augmentation Cystoplasty

Urinary Tract Infection

The urine may be colonized with Gram-negative bacteria, and attempts to sterilize the urine for prolonged periods usually fail. There is no evidence that chronic bacteriuria in patients who have had enterocystoplasty is associated with renal damage; therefore, only symptomatic UTIs should be treated.

Metabolic Acidosis

The enteric mucosal surface in contact with the urine absorbs ammonia, chloride, and hydrogen ions and loses potassium. Hyperchloremic metabolic acidosis can result, possibly requiring medical treatment (see Chapter 55). Chronic acidosis can compromise skeletal growth. This condition is common with colocystoplasty but is rare with ileocystoplasty. Metabolic acidosis also is common in patients with compromised renal function. To overcome this limitation of enterocystoplasty in patients with chronic renal insufficiency, a composite augmentation using stomach and small or large bowel gastric segment can be used. The stomach secretes chloride and hydrogen ions; thus, preexisting metabolic acidosis remains stable or improves.

Spontaneous Perforation

Perforation of the augmented bladder is a life-threatening complication that results most often from acute or chronic overdistention of the augmented bladder. Patients with this complication typically present with severe abdominal pain and signs of peritonitis. Prompt diagnosis and treatment with exploratory laparotomy and bladder closure are necessary. Meticulous adherence to the prescribed program of intermittent catheterization to avoid bladder overdistention is important.

Bladder Calculi

Bladder calculi have developed in as many as 70% of children followed for 10 yr after enterocystoplasty. The calculi develop in response to mucus that accumulates in the bladder and act as a nidus for stone formation. This complication can be prevented by daily irrigation of the bladder with sterile saline.

Malignant Neoplasm

Invasive transitional cell carcinoma has been reported in nearly 2% of patients undergoing enterocystoplasty (compared with a 1% risk in spina bifida patients without enterocystoplasty). The pathogenesis is uncertain but is speculated that it is related to bacteriuria and the bowel-bladder contact. The risk seems to be highest following gastrointestinal. The risk seems to increase 10 yr following enterocystoplasty. Although these patients probably should undergo screening, there are no guidelines or recommendations regarding this practice. It seems appropriate to advise yearly endoscopic examinations or urine cytologic studies beginning in the 10th postoperative year.

Future Management

The development of a tissue-engineered bladder using a composite scaffold, which could be attached to the dome of the bladder to increase capacity and compliance, might help patients achieve continence.

Figure 542-2 Voiding cystourethrogram in an infant with myelodysplasia shows a severely trabeculated bladder with multiple diverticula and grade V (out of V) right vesicoureteral reflux. Evaluation showed severe detrusor–sphincter dyssynergia.
ASSOCIATED DISORDERS

Constipation

Many patients with spina bifida also have bowel problems with constipation, and a vigorous bowel regimen is important. Some benefit from the **Malone antegrade continence enema procedure**, in which the appendix is brought out to the skin to allow a catheter to be inserted into the cecum for antegrade enema. The stoma is continent, and an antegrade enema can be performed with tap water each day. This form of management allows the patient to be continent of stool and be more self-sufficient.

**Latex Allergy**

Latex allergy is a very serious problem encountered by as many as half of patients with spina bifida and other urologic conditions who require clean intermittent catheterization and urinary tract reconstructive procedures. This immunoglobulin E–mediated allergy is acquired and is secondary to repeated exposure to the latex allergen. Latex allergy can manifest as watery eyes, sneezing, itching, hives, or anaphylaxis when blowing up a balloon or if an examiner is using latex gloves. Intraoperatively, a sensitized patient can experience anaphylactic shock. A latex-free environment should be provided for all children with spina bifida in the office, during hospitalization, and during operative procedures. Affected children also should wear a medical alert bracelet.

**Occult Spinal Dysraphism**

Approximately 1 in 4,000 patients have occult spinal dysraphism, a category that includes lipomeningocele, intradural lipoma, diastematomyelia, tight filum terminale, dermoid cyst-sinus, aberrant nerve roots, anterior sacral meningocele, and cauda equina tumor. More than 90% of patients have a cutaneous abnormality overlying the lower spine, including a small dimple, tuft of hair, dermal vascular malformation, or subcutaneous lipoma (Fig. 542-4). Often these children have high-arched feet, discrepancy in muscle size and strength between the legs, and a gait abnormality. Newborns and young infants often have a normal neurologic examination. Older children often have absent perineal sensation and back pain. Lower urinary tract function is abnormal in 40% of patients, including incontinence, recurrent UTI, and fecal soiling. The likelihood of a normal examination is inversely related to the child's age at surgical correction of the spinal lesion. In infants with abnormal urodynamics, 60% revert to normal; in older children, only 27% become normal. Management of the urinary tract in other children is similar to that described earlier for neural tube defects.

**Sacral Agenesis**

Sacral agenesis is defined as the absence of part or all of ≥2 lower vertebral bodies. This condition is more common in the offspring of women with diabetes. These children have a flattened buttock and a low, short gluteal cleft but usually have no orthopedic deformity, although some have high-arched feet. Palpation of the coccygeal area detects the absent vertebrae. Approximately 20% of cases are undetected until the age of 3-4 yr; many are diagnosed after unsuccessful
toilet training. Urodynamic studies in these children show a variety of patterns, and most need clean intermittent catheterization and pharmacotherapy to stay dry.

**Imperforate Anus**
Approximately 30-45% of children with a high imperforate anus have a neuropathic bladder, often because of sacral agenesis. Newborns with imperforate anus should undergo a spinal ultrasound during their initial evaluation, and if these children have difficulty with toilet training, complete urologic evaluation with upper and lower urinary tract imaging and urodynamics should be performed. See Chapter 344 for further details.

**Cerebral Palsy**
Children with cerebral palsy (see Chapter 598.1) often have reasonable bladder control. However, they achieve continence at a later age than unaffected children. Overall, 25-50% are incontinent, and the risk is directly related to the severity of physical impairment. Their upper urinary tracts usually are normal. Urodynamic studies have shown that most have uninhibited bladder contractions. Timed voiding and anticholinergic therapy are usually effective. Clean intermittent catheterization rarely is necessary.

*Bibliography is available at Expert Consult.*
Bibliography


NORMAL VOIDING AND TOILET TRAINING

Fetal voiding occurs by reflex bladder contraction in concert with simultaneous contraction of the bladder and relaxation of the sphincter. Urine storage results from sympathetic and pudendal nerve-mediated inhibition of detrusor contractile activity accompanied by closure of the bladder neck and proximal urethra with increased activity of the external sphincter. The infant has coordinated reflex voiding as often as 15-20 times/day. Over time, bladder capacity increases. In children up to the age of 14 yr, the mean bladder capacity in ounces is equal to the age (in years) plus 2.

At 2-4 yr, the child is developmentally ready to begin toilet training. To achieve conscious bladder control, several conditions must be present: awareness of bladder filling; cortical inhibition (suprapontine modulation) of reflex (unstable) bladder contractions; ability to consciously tighten the external sphincter to prevent incontinence; normal bladder growth; and motivation by the child to stay dry. The transitional phase of voiding refers to the period when children are acquiring bladder control. Girls typically acquire bladder control before boys, and bowel control typically is achieved before bladder control.

A common condition in children is bladder–bowel dysfunction. This term was coined by the American Urological Association Vesico-ureteral Reflux Guidelines Committee and refers to disorders of bladder and/or bowel function. The previous term for this condition was dysfunctional elimination syndrome.

DIURNAL INCONTINENCE

Daytime incontinence not secondary to neurologic abnormalities is common in children. The most common cause of daytime incontinence is an overactive bladder (urge incontinence). At age 5 yr, 95% have been dry during the day at some time and 92% are dry. At 7 yr, 96% are dry, although 15% have significant urgency at times. At 12 yr, 99% are dry during the day. Table 543-1 lists the causes of diurnal incontinence in children.

The history should assess the pattern of incontinence, including the frequency, the volume of urine lost during incontinent episodes, whether the incontinence is associated with urgency or giggling, whether it occurs after voiding, and whether the incontinence is continuous. The frequency of voiding and whether there is nocturnal enuresis, a strong, continuous urinary stream, or sensation of incomplete bladder emptying should be assessed. A diary of when the child voids and whether the child was wet or dry is helpful. Other urologic problems such as urinary tract infections (UTIs), vesicoureteral reflux, neurologic disorders, or a family history of duplication anomalies should be assessed. Bowel habits also should be evaluated, because incontinence is common in children with constipation and/or encopresis. Diurnal incontinence can occur in girls with a history of sexual abuse. Physical examination is directed at identifying signs of organic causes of incontinence: short stature, hypertension, enlarged kidneys and/or bladder, constipation, labial adhesion, ureteral ectopy, back or sacral anomalies (see Fig. 542-4 in Chapter 542), and neurologic abnormalities.

Assessment tools include urinalysis, with culture if indicated; bladder diary (recorded times and volumes voided, whether wet or dry); postvoid residual urine volume (generally obtained by bladder scan); and Dysfunctional Voiding Symptom Score (Fig. 543-1). An alternative to the Dysfunctional Voiding Symptom Score is the Vancouver Nonneurogenic Lower Urinary Tract Dysfunction/Dysfunctional Elimination Syndrome questionnaire. This questionnaire is a validated tool that consists of 14 questions scored on a 5-point Likert scale to assess lower urinary tract and bowel dysfunction. In most cases, a uroflow with or without electromyography (noninvasive assessment of urinary flow pattern and measurement of external sphincter activity) is indicated. Another item that may be useful in children older than age 5 yr is the Pediatric Symptom Checklist (PSC). The Pediatric Symptom Checklist is a brief screening questionnaire consisting of 35 questions that is used by pediatricians and other health professionals to improve the recognition and treatment of psychosocial problems in children.

Bowel function should be assessed also. The Bristol Stool Form Score (Fig. 543-2) also should be recorded. In addition, the clinician should utilize the Rome III diagnostic criteria, which classify functional gastrointestinal disorders that do not have underlying structural or tissue-based causes. Children 4 yr of age or older are diagnosed as being

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Table 543-1 Causes of Urinary Incontinence in Childhood

<table>
<thead>
<tr>
<th>Causes of Urinary Incontinence in Childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overactive bladder (urge incontinence)</td>
</tr>
<tr>
<td>Infrequent voiding (underactive bladder)</td>
</tr>
<tr>
<td>Voiding postponement</td>
</tr>
<tr>
<td>Detrusor–sphincter dyssynergia</td>
</tr>
<tr>
<td>Nonneurogenic neurogenic bladder (Hinman syndrome)</td>
</tr>
<tr>
<td>Vaginal voiding</td>
</tr>
<tr>
<td>Giggle incontinence</td>
</tr>
<tr>
<td>Cystitis</td>
</tr>
<tr>
<td>Bladder outlet obstruction (posterior urethral valves)</td>
</tr>
<tr>
<td>Ectopic ureter and fistula</td>
</tr>
<tr>
<td>Sphincter abnormality (epispadias, exstrophy; urogenital sinus abnormality)</td>
</tr>
<tr>
<td>Neuropathic</td>
</tr>
<tr>
<td>Overflow incontinence</td>
</tr>
<tr>
<td>Traumatic</td>
</tr>
<tr>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Behavioral</td>
</tr>
<tr>
<td>Combinations</td>
</tr>
</tbody>
</table>

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Urologic Disorders in Infants and Children

**Constipated** if they fulfill 2 or more of the following criteria over a period of 2 mo: 2 or fewer defecations in the toilet per week, at least 1 episode of fecal incontinence per week, a history of retentive posturing or excessive volitional stool retention, history of painful or hard bowel movements, presence of a large fecal mass in the rectum, and history of large-diameter stools that obstruct the toilet.

Imaging is performed in children who have significant physical findings, a family history of urinary tract anomalies or UTIs, and those who do not respond to therapy appropriately. A renal ultrasonogram with or without a voiding cystourethrogram is indicated. Urodynamics should be performed if there is evidence of neurologic disease and may be helpful if empirical therapy is ineffective. If there is any evidence of a neurologic disorder, an MRI of the lower spine should be obtained.

**OVERACTIVE BLADDER (DIURNAL URGE SYNDROME)**

Children with an overactive bladder typically exhibit urinary frequency, urgency, and urge incontinence. Often a girl will squat down on her foot to try to prevent incontinence (termed Vincent's curtsy). The bladder in these children is functionally, but not anatomically, smaller than normal and exhibits strong uninhibited contractions. Approximately 25% of children with nocturnal enuresis also have symptoms of an overactive bladder. Many children indicate they do not feel the need to urinate, even just before they are incontinent. In girls, a history of recurrent UTI is common, but incontinence can persist long after infections are brought under control. It is not clear if the voiding dysfunction is a sequela of the UTIs or if the voiding dysfunction predisposes to recurrent UTIs. In girls, voiding cystourethrography often shows a dilated urethra ("spinning-top deformity," Fig. 543-3) and narrowed bladder neck with bladder wall hypertrophy. The urethral finding results from inadequate relaxation of the external sphincter.}

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<table>
<thead>
<tr>
<th>Over the last month</th>
<th>Almost never</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>Almost every time</th>
<th>Not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have had wet clothes or wet underwear during the day</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>2. When I wet myself, my underwear is soaked.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>3. I miss having a bowel movement every day.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>4. I have to push for my bowel movements to come out.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>5. I only go to the bathroom one or two times each day.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>6. I can hold onto my pee by crossing my legs, squatting or doing the &quot;pee dance.&quot;</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>7. When I have to pee, I cannot wait.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>8. I have to push to pee.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>9. When I pee it hurts.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>10. Parents to answer. Has your child experienced something stressful like the example below?</td>
<td>No (0)</td>
<td>Yes (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total* females with a score ≥6 and males with a score ≥9 are most likely to have dysfunctional voiding.

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**Figure 543-2** Bristol Stool Chart for evaluating bowel function.
urinary sphincter. Constipation is common and should be treated, particularly with any child with Bristol Stool Score 1 or 2.

The overactive bladder nearly always resolves, but the time to resolution is highly variable, sometimes not until the teenage years. Initial therapy is timed voiding, every 1.5-2.0 hr. Treatment of constipation and UTIs is important. Another treatment is biofeedback, in which children are taught pelvic floor exercises (Kegel exercises), because there is evidence that daily performance of these exercises can reduce or eliminate unstable bladder contractions. Biofeedback often includes participation with animated computer games. Biofeedback also may include periodic uroflow studies with sphincter electromyography to be certain that the pelvic floor relaxes during voiding, and assessment of postvoid residual urine volume by sonography. Anticholinergic therapy with oxybutynin chloride, hyoscyamine, or tolterodine reduces bladder overactivity and may help the child achieve dryness. Treatment with an α-adrenergic blocker such as terazosin or doxazosin can aid in bladder emptying by promoting bladder neck relaxation; α-adrenergic blockers also have mild anticholinergic properties. If pharmacologic therapy is successful, the dosage should be tapered periodically to determine its continued need. Children who do not respond to therapy should be evaluated urodynamically to rule out other possible forms of bladder or sphincter dysfunction. In refractory cases, sacral nerve stimulation (InterStim) is a surgical procedure that has shown promise.

If the child has constipation based on the criteria described above, treatment generally is initiated with polyethylene glycol powder, which has been shown to be safe in children and generally more effective than other laxative preparations.

NONNEUROGENIC NEUROGENIC BLADDER (HINMAN SYNDROME)

Hinman syndrome is a very serious but uncommon disorder involving failure of the external sphincter to relax during voiding in children without neurologic abnormalities. Children with this syndrome, also called nonneurogenic neurogenic bladder, typically exhibit a staccato stream, day and night wetting, recurrent UTIs, constipation, and encopresis. Evaluation of affected children often reveals vesicoureteral reflux, a trabeculated bladder, and a decreased urinary flow rate with an intermittent pattern (Fig. 543-4). In severe cases, hydronephrosis, renal insufficiency, and end-stage renal disease can occur. The pathogenesis of this syndrome is thought to involve learning abnormal voiding habits during toilet training; the syndrome is rarely seen in infants. Urodynamic studies and magnetic resonance imaging of the spine are indicated to rule out a neurologic cause for the bladder dysfunction.

The treatment usually is complex and can include anticholinergic and α-adrenergic blocker therapy, timed voiding, treatment of constipation, behavioral modification, and encouragement of relaxation during voiding. Biofeedback has been used successfully in older children to teach relaxation of the external sphincter. In some cases botulinum toxin (Botox) injection into the external sphincter can provide temporary sphincteric paralysis and thereby reduce outlet resistance. In severe cases, intermittent catheterization is necessary to ensure bladder emptying. In selected patients, external urinary diversion is necessary to protect the upper urinary tract. These children require long-term treatment and careful follow-up.

INFREQUENT Voiding (UNDERACTIVE BLADDER)

Infrequent voiding is a common disorder of micturition, usually associated with UTIs. Affected children, usually girls, void only twice a day rather than the normal 4-7 times. With bladder overdistention and prolonged retention of urine, bacterial growth can lead to recurrent UTIs. Some of these children are constipated. Some also have occasional episodes of incontinence from overflow or urgency. The disorder is behavioral. If the child has UTIs, treatment includes antibacterial prophylaxis and encouragement of frequent voiding and complete emptying of the bladder by double voiding until a normal pattern of micturition is re-established.

VAGINAL VOIDING

In girls with vaginal voiding, incontinence typically occurs after urination after the girl stands up. Usually the volume of urine is 5-10 mL. One of the most common causes is labial adhesion (Fig. 543-5). This lesion, typically seen in young girls, can be managed either by topical application of estrogen cream to the adhesion or lysis in the office. Some girls experience vaginal voiding because they do not separate their legs widely during urination. These girls either are overweight
or do not pull their underwear down to their ankles when they urinate. Management involves encouraging the girl to separate the legs as widely as possible during urination. The most effective way to do this is to have the child sit backward on the toilet seat during micturition.

**OTHER CAUSES OF INCONTINENCE IN GIRLS**

Ureteral ectopia, usually associated with a duplicated collecting system in girls, refers to a ureter that drains outside the bladder, often into the vagina or distal urethra. It can produce urinary incontinence characterized by constant urinary dripping all day, even though the child voids regularly. Sometimes the urine production from the renal segment drained by the ectopic ureter is small, and urinary drainage is confused with watery vaginal discharge. Children with a history of vaginal discharge or incontinence and an abnormal voiding pattern require careful study. The ectopic orifice usually is difficult to find. On ultrasonography or intravenous urography, one may suspect duplication of the collecting system (Fig. 543-6), but the upper collecting system drained by the ectopic ureter usually has poor or delayed function. CT scanning of the kidneys or an MR urogram should demonstrate subtle duplication anomalies. Examination under anesthesia for an ectopic ureteral orifice in the vestibule or the vagina may be necessary (Fig. 543-7). The treatment in these cases is either partial nephrectomy, with removal of the upper pole segment of the duplicated kidney and its ureter down to the pelvic brim, or ipsilateral ureteroureterostomy, in which the upper pole ectopic ureter is anastomosed to the normally positioned lower pole ureter. These procedures often are performed by minimally invasive laparoscopy with or without robotic assistance.

Giggle incontinence typically affects girls 7-15 yr of age. The incontinence occurs suddenly during giggling, and the entire bladder volume is lost. The pathogenesis is thought to be sudden relaxation of the urinary sphincter. Anticholinergic medication and timed voiding occasionally are effective. The most effective treatment is low-dose methylphenidate.

Total incontinence in girls may be secondary to epispadias (see Fig. 541-2 in Chapter 541). This condition, which affects only 1 in 480,000 females, is characterized by separation of the pubic symphysis, separation of the right and left sides of the clitoris, and a patulous urethra. Treatment is bladder neck reconstruction or placement of an artificial urinary sphincter to repair the incompetent urethra.

A short, incompetent urethra may be associated with certain genital sinus malformations. The diagnosis of these malformations requires a high index of suspicion and a careful physical examination of all incontinent girls. In these cases, urethral and vaginal reconstruction often restores continence.

**VOIDING DISORDERS WITHOUT INCONTINENCE**

Some children have abrupt onset of severe urinary frequency, voiding as often as every 10-15 min during the day, without dysuria, UTI, daytime incontinence, or nocturia. The most common age for these symptoms to occur is 4-6 yr, after the child is toilet trained, and the vast majority are boys. This condition is termed the **daytime frequency syndrome of childhood** or pollakiuria. The condition is functional;
no anatomic problem is detected. Often the symptoms occur just before a child starts kindergarten or if the child is having emotional family stress-related problems. These children should be checked for UTIs, and the clinician should ascertain that the child is emptying the bladder satisfactorily. Occasionally, pinworms cause these symptoms. The condition is self-limited, and symptoms generally resolve within 2-3 mo. Anticholinergic therapy rarely is effective.

Some children have the dysuria-hematuria syndrome, in which the child has dysuria without UTI but with microscopic or gross hematuria. This condition affects children who are toilet-trained and is often secondary to hypercalciuria. A 24-hr urine sample should be obtained and calcium and creatinine excretion assessed. A 24-hr calcium excretion of >4 mg/kg is abnormal and deserves treatment with thiazides, because some of these children are at risk for urolithiasis.

**NOCTURNAL ENURESIS**

By 5 yr of age, 90-95% of children are nearly completely continent during the day, and 80-85% are continent at night. Nocturnal enuresis refers to the occurrence of involuntary voiding at night after 5 yr, the age when volitional control of micturition is expected. Enuresis may be primary (estimated 75-90% of children with enuresis; nocturnal urinary control never achieved) or secondary (10-25%; the child was dry at night for at least a few months and then enuresis developed). In addition, 75% of children with enuresis are wet only at night, and 25% are continent day and night. This distinction is important, because children with both forms are more likely to have an abnormality of the urinary tract. Monosymptomatic enuresis is more common than nonmonosymptomatic enuresis (associated urgency, hesitancy, frequency, day time incontinence).

**Epidemiology**

Approximately 60% of children with nocturnal enuresis are boys. Family history is positive in 50% of cases. Although primary nocturnal enuresis may be polygenic, candidate genes have been localized to chromosomes 12 and 13. If one parent was enuretic, each child has a 44% risk of enuresis; if both parents were enuretic, each child has a 77% likelihood of enuresis. Nocturnal enuresis without overt daytime voiding symptoms affects up to 20% of children at the age of 5 yr; it ceases spontaneously in approximately 15% of involved children every year thereafter. Its frequency among adults is <1%.

**Pathogenesis**

The pathogenesis of nocturnal enuresis (normal daytime voiding habits) is multifactorial (Table 543-2).

**Clinical Manifestations and Diagnosis**

A careful history should be obtained, especially with respect to fluid intake at night and pattern of nocturnal enuresis. Children with diabetes insipidus (see Chapter 558), diabetes mellitus (see Chapter 589), and chronic renal disease (see Chapter 535) can have a high obligatory urinary output and a compensatory polydipsia. The family should be asked whether the child snores loudly at night. A complete physical examination should include palpation of the abdomen and rectal examination after voiding to assess the possibility of a chronically distended bladder. The child with nocturnal enuresis should be examined carefully for neurologic and spinal abnormalities. There is an increased incidence of bacteriuria in enuretic girls, and, if found, it should be investigated and treated (see Chapter 538), although this does not always lead to resolution of bedwetting. A urine sample should be obtained after an overnight fast and evaluated for specific gravity or osmolality to exclude polyuria as a cause of frequency and incontinence and to ascertain that the concentrating ability is normal. The absence of glycosuria should be confirmed. If there are no daytime symptoms, the physical examination and urinalysis are normal, and the urine culture is negative, further evaluation for urinary tract pathology generally is not warranted. A renal ultrasonogram is reasonable in an older child with enuresis or in children who do not respond appropriately to therapy.

**Treatment**

The best approach to treatment is to reassure the child and parents that the condition is self-limited and to avoid punitive measures that can affect the child's psychologic development adversely. Fluid intake should be restricted to 2 oz after 6 or 7 PM. The parents should be certain that the child voids at bedtime. Avoiding extraneous sugar and caffeine after 4 PM also is beneficial. If the child snores and the adenoids are enlarged, referral to an otolaryngologist should be considered, because adenoidectomy can cure the enuresis.

**Table 543-2 Nocturnal Enuresis**

<table>
<thead>
<tr>
<th>CAUSES</th>
</tr>
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<tbody>
<tr>
<td>Delayed maturation of the cortical mechanisms that allow voluntary control of the micturition reflex</td>
</tr>
<tr>
<td>Defective sleep arousal</td>
</tr>
<tr>
<td>Reduced antidiuretic hormone production at night, resulting in an increased urine output (nocturnal polyuria)</td>
</tr>
<tr>
<td>Genetic factors, with chromosomes 12 and 13q the likely sites of the gene for enuresis</td>
</tr>
<tr>
<td>Bladder factors (lack of inhibition, reduced capacity, overactive)</td>
</tr>
<tr>
<td>Organic factors, such as urinary tract infection or obstructive uropathy</td>
</tr>
<tr>
<td>Sleep disorders</td>
</tr>
<tr>
<td>Sleep disordered breathing secondary to enlarged adenoids</td>
</tr>
<tr>
<td>Psychologic factors more often implicated in secondary enuresis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enuresis can occur in any stage of sleep (but usually non–rapid eye movement sleep)</td>
</tr>
<tr>
<td>All children are most difficult to arouse in the first third of the night and easiest to awaken in the last third, but enuretic children are more difficult to arouse than those with normal bladder control</td>
</tr>
<tr>
<td>Enuretic children often are described as “soaking the bed”</td>
</tr>
<tr>
<td>Family history in enuretic children often positive for enuresis</td>
</tr>
<tr>
<td>Risk increased with developmental delay, attention-deficit/hyperactivity disorder, autism spectrum disorders</td>
</tr>
</tbody>
</table>

**Figure 543-7** This photograph shows an ectopic ureter entering the vestibule next to the urethral meatus. The thin ureteral catheter with transverse marks has been introduced into this ectopic ureter. This girl had a normal voiding pattern and constant urinary dribbling.
Active treatment should be avoided in children younger than 6 yr of age, because enuresis is extremely common in younger children. Treatment is more likely to be successful in children approaching puberty compared with younger children. In addition, treatment is most likely to be effective in children who are motivated to stay dry. Treatment should be viewed as a facilitator that requires active participation by the child (e.g., a coach and an athlete).

The simplest initial measure is motivational therapy and includes a star chart for dry nights. Waking children a few hours after they go to sleep to have them void often allows them to awaken dry, although this measure is not curative. Some have recommended that children try holding their urine for longer periods during the day, but there is no evidence that this approach is beneficial. Conditioning therapy involves use of a loud auditory or vibratory alarm attached to a moisture sensor in the underwear. The alarm sounds when voiding occurs and is intended to awaken children and alert them to void. This form of therapy has a reported success of 30-60%, although the relapse rate is significant. Often the auditory alarm wakes up other family members and not the enuretic child; persistent use of the alarm for several months often is necessary to determine whether this treatment is effective. Conditioning therapy tends to be most effective in older children.

Another form of therapy to which some children respond is self-hypnosis. The primary role of psychologic therapy is to help the child deal with enuresis psychologically and help motivate the child to void at night if he or she awakens with a full bladder.

Pharmacologic therapy is intended to treat the symptom of enuresis and thus is regarded as second line and is not curative. Direct comparisons of the bell and bed with pharmacologic therapy favor the former because of lower relapse rates, although initial response rates are equivalent.

One form of treatment is desmopressin acetate, a synthetic analog of antidiuretic hormone that reduces urine production overnight. This medication is FDA-approved and is available as a tablet, with a dosage of 0.2-0.6 mg at bedtime. In the past a nasal spray was used, but some children experienced hyponatremia and convulsions with this formulation and the nasal spray is no longer recommended for nocturnal enuresis. Hyponatremia has not been reported in children using the oral tablets. Fluid restriction at night is important, and the drug should not be used if the child has a systemic illness with vomiting or diarrhea or if the child has polydipsia. Desmopressin acetate is effective in as many as 40% of children. If effective, it should be used for 3-6 mo, and then an attempt should be made to taper the dosage. If tapering results in recurrent enuresis, the child should return to the higher dosage. Few adverse events have been reported with the long-term use of desmopressin acetate.

For therapy-resistant enuresis or children with symptoms of an overactive bladder, anticholinergic therapy is indicated. Oxybutynin 5 mg or tolterodine 2 mg at bedtime often are prescribed. If the medication is ineffective, the dosage may be doubled. The clinician should monitor for constipation as a potential side effect.

A third-line treatment is imipramine, which is a tricyclic antidepressant. This medication has mild anticholinergic and α-adrenergic effects, reduces urine output slightly, and also might alter the sleep pattern. The dosage of imipramine is 25 mg in children age 6-8 yr, 50 mg in children age 9-12 yr, and 75 mg in teenagers. Reported success rates are 30-60%. Side effects include anxiety, insomnia, and dry mouth, and heart rhythm may be affected. If there is any history of palpitations or syncope in the child, or sudden cardiac death or unstable arrhythmia in the family, long QT syndrome in the patient needs to be excluded. The drug is one of the most common causes of poisoning by prescription medication in younger siblings.

In unsuccessful cases, combining therapies often is effective. Alarm therapy plus desmopressin is more successful than either alone. The combination of oxybutynin chloride and desmopressin is more successful than either alone. Desmopressin and imipramine also may be combined.

Bibliography is available at Expert Consult.
Bibliography

HYPOSPADIAS

Hypospadias is a urethral opening on the ventral surface of the penile shaft affecting 1 in 250 male newborns. Typically an isolated defect, but its incidence is increased in disorders of sex differentiation, anorectal malformation, and congenital heart disease. Usually there is incomplete development of the prepuce, called a dorsal hood, in which the foreskin is on the sides and dorsal aspect of the penile shaft and deficient or absent ventrally. Some boys with hypospadias, particularly those with proximal hypospadias, have chordee, in which there is ventral penile curvature during erection. The incidence of hypospadias appears to be increasing, possibly because of in utero exposure to estrogenic or antiandrogenic endocrine-disrupting chemicals (e.g., polychlorobiphenyls, phytoestrogens).

Clinical Manifestations

Hypospadias is classified according to the position of the urethral meatus after taking into account whether chordee is present (Fig. 544-1). The deformity is described as glanular (on the glans penis), coronal, subcoronal, midpenile, penoscrotal, scrotal, or perineal. Approximately 65% of cases are distal, 25% are subcoronal or midpenile, and 10% are proximal. In the most severe cases, the scrotum is bifid and sometimes there is moderate penoscrotal transposition. As many as 10% of affected boys have a megameatal variant, in which the foreskin is developed normally (megameatus intact prepuce variant), and there is either glanular or subcoronal hypospadias with a “fish mouth” meatus. These cases might not be diagnosed until after a circumcision is performed.

Approximately 10% of boys with hypospadias have an undescended testis; inguinal hernias also are common. In the newborn, the differential diagnosis of midpenile or proximal hypospadias associated with an undescended testis should include forms of a disorder of sex development, particularly mixed gonadal dysgenesis, partial androgen insensitivity, true hermaphroditism, and congenital adrenal hyperplasia in a female (see Chapter 576). In the latter situation, neither gonad would be palpable. A karyotype should be obtained in patients with midpenile or proximal hypospadias and cryptorchidism (see Chapter 588). In boys with penoscrotal hypospadias, a voiding cystourethrogram should be considered because 5-10% of these children have a dilated prostatic utricle, which is a remnant of the müllerian system (see Chapter 554). The incidence of upper urinary tract abnormalities is low unless there are abnormalities of other organ systems.

Complications of untreated hypospadias include deformity of the urinary stream, typically ventral deflection or severe splaying; sexual dysfunction secondary to penile curvature; infertility if the urethral meatus is proximal; meatal stenosis (congenital), which is uncommon; and cosmetic appearance. The goal of hypospadias surgery is to correct the functional and cosmetic deformities. Whereas hypospadias repair is recommended for all boys with midpenile and proximal hypospadias, some boys with distal hypospadias have no functional abnormality and do not need any surgical correction.

Treatment

Management begins in the newborn period. Circumcision should be avoided, because the foreskin often is used in the repair in most cases. The ideal age for repair in a healthy infant is 6-12 mo, because the risk of general anesthesia at this age is similar to older children; penile growth over the next several years is slow; the child does not remember the surgical procedure; and postoperative analgesic needs are less than
in older children. With the exception of proximal hypospadias, virtually all cases are repaired in a single operation on an ambulatory basis. The most common repair involves tubularization of the urethral plate distal to the urethral meatus, with coverage by a vascularized flap from the foreskin, termed a tubularized incised plate repair. Proximal cases might require a 2-stage repair. The complication rate is low: 5% for distal hypospadias, 10% for midpenile hypospadias, and 20% for proximal hypospadias. The most common complications include urethrocutaneous fistula and meatal stenosis. Other complications include a deformed urinary stream, persistent penile curvature, and dehiscence of the hypospadias repair. Treatment of these complications generally is straightforward. In complex cases, a buccal mucosa graft is used to create urethral mucosa. Repair of hypospadias is a technically demanding operation and should be performed by a surgeon with specialty training in pediatric urology and extensive experience.

**CHORDEE WITHOUT HYPOSPADIAS**

In some boys there is mild or moderate ventral penile curvature (chordee) and incomplete development of the foreskin (dorsal hood), but the urethral meatus is at the tip of the glans (Fig. 544-2). In most of these boys, the urethra is normal but there is insufficient ventral penile skin or prominent, inelastic ventral bands of dartos fascia that prevent a straight erection. In some cases, the urethra is hypoplastic, and a formal urethroplasty is necessary for repair. The only sign of this anomaly in the neonate may be the hooded foreskin, and delayed repair under general anesthesia at 6 mo of age is recommended.

**PHIMOSIS AND PARAPHIMOSIS**

Phimosis refers to the inability to retract the prepuce. At birth, phimosis is physiologic. Over time, the adhesions between the prepuce and glans lyse and the distal phimotic ring loosens. In 80% of uncircumcised boys the prepuce becomes retractable by 3 yr of age. Accumulation of epithelial debris under the infant’s prepuce is physiologic and does not mandate circumcision. In older boys, phimosis may be physiologic, may be pathologic from inflammation and scarring at the tip of the foreskin (Fig. 544-3), or occurs after circumcision. The prepuce might have been retracted forcefully on 1 or 2 occasions in the past, which can result in a cicatricial scar that prevents subsequent retraction of the foreskin. In boys with persistent physiologic or pathologic phimosis, application of corticosteroid cream to the foreskin 3 times daily for 1 mo loosens the phimotic ring in two-thirds of cases. The complication rate is low: 5% for distal hypospadias, 10% for midpenile hypospadias, and 20% for proximal hypospadias. The most common complications include urethrocutaneous fistula and meatal stenosis. Other complications include a deformed urinary stream, persistent penile curvature, and dehiscence of the hypospadias repair. Treatment of these complications generally is straightforward. In complex cases, a buccal mucosa graft is used to create urethral mucosa. Repair of hypospadias is a technically demanding operation and should be performed by a surgeon with specialty training in pediatric urology and extensive experience.

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hyaluronidase into the edematous skin has been reported to result in immediate reduction in swelling. In rare cases, emergency circumcision under general anesthesia is necessary.

**CIRCUMCISION**

In the United States, circumcision usually is performed for cultural reasons. In 2012, a multidisciplinary task force of the American Academy of Pediatrics stated that evidence indicates that the health benefits of newborn male circumcision outweigh the risks and that the procedure's benefits justify access to this procedure for families who choose it. Specific benefits identified included prevention of urinary tract infections (UTIs), penile cancer, reducing the risk and transmission of some sexually transmitted infections, including HIV. The American College of Obstetricians and Gynecologists endorsed this policy statement. By contrast, European medical professional groups have been less likely to endorse this practice.

When performing a neonatal circumcision, local analgesia, such as a dorsal nerve block or application of EMLA (eutectic mixture of local anesthetics) cream (lidocaine 2.5% and prilocaine 2.5%) is recommended.

UTIs are 10-15 times more common in uncircumcised infant boys than in circumcised infants, with the urinary pathogens arising from bacteria that colonize the space between the prepuce and glans. The risk of febrile UTI (see Chapter 538) is highest between birth and 6 mo, but there is an increased risk of UTI until at least 5 yr of age. Many recommend circumcision in infants who are predisposed to UTI, such as those with congenital hydronephrosis and vesicoureteral reflux. Circumcision reduces the risk of sexually transmitted infections in adults (see Chapter 120), in particular HIV (see Chapter 276). There have been only a handful of reports of men who were circumcised at birth and subsequently acquired penile carcinoma, but in Scandinavian countries, where few men are circumcised and hygiene is good, the incidence of penile cancer is low.

Complications after neonatal circumcision include bleeding, wound infection, meatal stenosis, secondary phimosis, removal of insufficient foreskin, and fibrous penile adhesions (skin bridge; Fig. 544-5); 0.2-3.0% of patients undergo a subsequent operative procedure. Boys with a large hydrocele or hernia are at particular risk for secondary phimosis because the scrotal swelling tends to displace the penile shaft skin over the glans. Potentially serious complications include sepsis, amputation of the distal part of the glans, removal of an excessive amount of foreskin, and urethrocrotaneous fistula. Circumcision should not be performed in neonates with hypospadias, chordee without hypospadias, or a dorsal hood deformity (relative contraindication) or in those with...
Anomalies of the Penis and Urethra

Chapter 544

A small penis (Fig. 544-6). In boys with a wandering raphe (Fig. 544-6), in which the median raphe deviates to 1 side, there may be underlying penile torsion or hypospadias, and evaluation by a pediatric urologist is suggested before performing a circumcision.

**PENILE TORSION**

Penile torsion, a rotational defect of the penile shaft, usually occurs in a counterclockwise direction (to the left side; see Fig. 544-6). In most cases, penile development is normal, and the condition is unrecognized until circumcision is performed or the foreskin is retractable. In many cases the midline raphe of the penile shaft is deviated. Penile torsion also occurs in some boys with hypospadias. The defect has primarily cosmetic significance and correction is unnecessary if the rotation is <60 degrees from the midline.

**INCONSPICUOUS PENIS**

The term inconspicuous penis refers to a penis that appears to be small. A webbed penis is a condition in which the scrotal skin extends onto the ventral penile shaft. This deformity represents an abnormality of the attachment between the penis and scrotum. Although the deformity might appear mild, if a routine circumcision is performed, the penis can retract into the scrotum, resulting in secondary phimosis (trapped penis). The concealed (hidden or buried) penis is a normally developed penis that is camouflaged by the suprapubic fat pad (Fig. 544-7). This anomaly may be congenital, iatrogenic after circumcision, or a result of obesity. Surgical correction is indicated for cosmetic reasons or if there is a functional abnormality with a splayed stream.

A trapped penis is an acquired form of inconspicuous penis and refers to a phallus that becomes embedded in the suprapubic fat pad after circumcision (Fig. 544-8). This deformity can occur after neonatal circumcision in an infant who has significant scrotal swelling from a large hydrocele or inguinal hernia or after routine circumcision in an infant with a webbed penis. This complication can predispose to UTIs and can cause urinary retention. Initial treatment of a trapped penis should include topical corticosteroid cream, which often loosens the phimotic ring. In some cases secondary repair is necessary at 6-9 mo.

**MICROPENIS**

Micropenis is defined as a normally formed penis that is at least 2.5 SD below the mean in size (Fig. 544-9). Typically, the ratio of the length...
of the penile shaft to its circumference is normal. The pertinent measurement is the **stretched penile length**, which is measured by stretching the penis and measuring the distance from the penile base under the pubic symphysis to the tip of the glans. The mean length of the term newborn penis is 3.5 ± 0.7 cm and the diameter is 1.1 ± 0.2 cm. The diagnosis of micropenis is made if the stretched length is <1.9 cm.

Micropenis usually results from a hormonal abnormality that occurs after 14 wk of gestation. Common causes include hypogonadotropic hypogonadism, hypergonadotropic hypogonadism (primary testicular failure), and idiopathic micropenis. If growth hormone deficiency also is present, neonatal hypoglycemia can occur. The most common cause of micropenis is failure of the hypothalamus to produce an adequate amount of gonadotropin-releasing hormone, as typically occurs in Kallmann syndrome (see Chapter 583), Prader-Willi syndrome (see Chapter 108), and Lawrence-Moon-Bardet-Biedl syndrome. In some cases, there is growth hormone deficiency. Primary testicular failure can result from gonadal dysgenesis or rudimentary testes syndrome and also occurs in Robinow syndrome (characterized by hypoplastic genitalia, shortening of the forearms, frontal bossing, hypertelorism, wide palpebral fissures, short broad nose, long philtrum, small chin, brachydactyly, and a normal karyotype).

A pediatric endocrinologist, geneticist, and pediatric urologist should examine all children with these syndromes. **Evaluation** includes a karyotype, assessment of anterior pituitary function and testicular function, and MRI to determine the anatomic integrity of the hypothalamus and the anterior pituitary gland as well as the midline structure of the brain. One of the difficult questions is whether androgen therapy is essential during childhood, because androgenic stimulation of penile growth in a prepubertal boy can limit the growth potential of the penis in puberty. Studies of small groups of men with micropenis suggest that many, although not all, have satisfactory sexual function. Consequently, a decision for gender reassignment is made infrequently.

**PRIAPISM**

Priapism is a persistent penile erection at least 4 hr in duration that continues beyond, or is unrelated to, sexual stimulation. Typically, only the corpora cavernosa are affected. There are 3 subtypes:

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**Figure 544-7** Concealed penis (A), which may be visualized by retracting skin lateral to penile shaft (B). (From Wein AJ, Kavoussi LR, Novick AC, et al, editors: Campbell-Walsh urology, ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-4, p. 2339.)

**Figure 544-9** Micropenis secondary to hypopituitarism in an 8-year-old boy. (From Wein AJ, Kavoussi LR, Novick AC, et al, editors: Campbell-Walsh urology, ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-5a, p. 2341.)

**Figure 544-8** A, Trapped (concealed) penis resulting from circumcision. B, Same patient after revision of circumcision. (From Wein AJ, Kavoussi LR, Novick AC, et al, editors: Campbell-Walsh urology, ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-2, p. 2340.)
Ischemic (venoocclusive, low-flow) priapism is characterized by little or no cavernous blood flow, and cavernous blood gases are hypoxic, hypercapnic, and acidic. The corpora are rigid and tender to palpation.

Nonischemic (arterial, high-flow) priapism is caused by unregulated cavernous arterial inflow. Typically, the penis is neither fully rigid nor painful. There is often a history of antecedent trauma resulting in a cavernous artery–corpora cavernosa fistula.

Stuttering (intermittent) priapism is a recurrent form of ischemic priapism with painful erections with intervening periods of detumescence.

The most common cause of priapism in children is sickle cell disease, which is characterized by predominance of sickle cell hemoglobin (see Chapter 462.1). As many as 27.5% of children with sickle cell disease develop priapism. The priapism is generally related to a low-flow state, secondary to sickling of red blood cells within the sinuses of the corpora cavernosa during normal erection, resulting in venous stasis. This situation results in decreased local oxygen tension and pH, which potentiates further stasis and sickness. Priapism typically occurs during sleep, when mild hyperventilation acidosis depresses oxygen tension and pH in the corpora. There is typically significant corporal engorgement with sparing of the glans penis. If the spongiosum is involved, voiding may be impaired. Evaluation includes complete blood count and serum chemistry. If sickle cell status is unknown, hemoglobin electrophoresis should be performed. In some cases, corporal aspiration is performed to distinguish between a high-flow and low-flow state. Other causes of low-flow priapism include sildenafil ingestion and leukemia.

In priapism secondary to sickle cell disease, medical therapy includes exchange transfusion, intravenous hydration, alkalinization, pain management with morphine, and oxygen. The American Urological Association guideline on priapism also recommends concurrent intracavernous treatment beginning with corporal aspiration and irrigation with a sympathomimetic agent, such as phenylephrine. If priapism has been present >48 hr, ischemia and acidosis impair the intracavernous smooth muscle response to sympathomimetics. If irrigation and medical therapy are unsuccessful, a corporoglanular shunt should be considered. For stuttering priapism, administration of an oral α-adrenergic agent (pseudoephedrine) once or twice daily is first-line therapy. If this treatment is unsuccessful, an oral β-agonist (terbutaline) is recommended; a gonadotropin-releasing hormone analog plus flutamide is recommended as third-line therapy. Long-term follow-up of adults treated for sickle cell disease as children shows that satisfactory erectile function is inversely related to the patient’s age at onset of priapism and duration of priapism.

Nonischemic (high-flow) priapism most commonly follows perineal trauma, such as a straddle injury, that results in laceration of the cavernous artery. Typically, the aspirated blood is bright red, and the aspirate is similar to arterial blood. Color Doppler ultrasonography often demonstrates the fistula. The priapism can spontaneously resolve. If it does not, angiographic embolization is indicated.

**OTHER MALE URETHRAL ANOMALIES**

**Paramesetal urethral cyst** manifests as an asymptomatic small cyst on one side of the urethral meatus. Treatment is excision under anesthesia. **Congenital urethral fistula** is a rare deformity in which a fistula is present from the penile urethra. It usually is an isolated abnormality. Treatment is fistula closure. **Megalourethra** is a large urethra that usually is associated with abnormal development of the corpus spongiosum. This condition is most commonly associated with prune-belly syndrome (see Chapter 540). **Urethral duplication** is a rare condition in which the 2 urethral channels lie in the same sagittal plane. There are many variations with complete and incomplete urethral duplication. These boys often have a double stream. Most commonly the dorsal urethra is small and the ventral urethra is normal caliber. Treatment involves excision of the small urethra. **Urethral hypoplasia** is a rare condition in which the urethra is extremely small but patent. In some cases, a temporary cutaneous vesicostomy is necessary for satisfactory urinary drainage. Either gradual enlargement of the urethra or major urethroplasty is necessary. **Urethral atresia** refers to maldevelopment of the urethra and nearly always is fatal unless the urachus remains patent throughout gestation.

**URETHRAL PROLAPSE (FEMALE)**

Urethral prolapse is encountered predominantly in black girls 1-9 yr of age. The most common signs are bloody spotting on the underwear or diaper, although dysuria or perineal discomfort also can occur (Fig. 544-10). An inexperienced examiner can mistake the finding for sexual
abuse. The usual therapy consists of application of estrogen cream 2-3 times daily for 3-4 wk and sitz baths. Surgical excision and reapproximation of the mucosal edges is recommended for girls that fail medical therapy and is curative.

OTHER FEMALE URETHRAL LESIONS

Paraurethral cyst results from retained secretions in the Skene glands secondary to ductal obstruction (Fig. 544-11). These lesions are present at birth, and most regress in size during the 1st 4-8 wk, although occasionally incision and drainage is necessary. A prolapsed ectopic ureterocele appears as a cystic mass protruding from the urethra and is a presenting symptom in 10% of girls with a ureterocele, which is a cystic swelling of the terminal ureter (Fig. 544-12). Ultrasonography should be performed to visualize the upper urinary tracts to confirm the diagnosis. Usually, either the ureterocele is incised or an upper urinary tract reconstructive procedure is necessary.

Bibliography is available at Expert Consult.
**Chapter 544  Anomalies of the Penis and Urethra**

**Bibliography**


UNDESCENDED TESTIS (CRYPTORCHIDISM)
The absence of a palpable testis in the scrotum indicates that the testis is undescended, absent, or retractile.

Epidemiology
An undescended (cryptorchid) testis is the most common disorder of sexual differentiation in boys. At birth, approximately 4.5% of boys have an undescended testis. Because testicular descent occurs at 7-8 mo of gestation, 30% of premature male infants have an undescended testis; the incidence is 3.4% at term. The majority of congenital undescended testes descend spontaneously during the 1st 3 mo of life, and by 6 mo the incidence decreases to 0.8%. Spontaneous descent occurs secondary to a temporary testosterone surge during the 1st 2 mo, which also results in significant penile growth. If the testis has not descended by 4 mo, it will remain undescended. Cryptorchidism is bilateral in 10% of cases. There is some evidence that the incidence of cryptorchidism is increasing. Although cryptorchidism usually is considered to be congenital, some boys have a scrotal testis that "ascends" to a low inguinal position, and therefore requires an orchio-pexy. In addition, 1-2% of neonatal and young boys undergoing hernia repair have secondary cryptorchidism.

Pathogenesis
The process of testicular descent is regulated by an interaction between hormonal and mechanical factors, including testosterone, dihydrotestosterone, müllerian-inhibiting factor, the gubernaculum, intraabdominal pressure, and the genitofemoral nerve. The testis develops at 7-8 wk of gestation. At 10-11 wk, the Leydig cells produce testosterone, which stimulates differentiation of the wolffian (mesonephric) duct into the epididymis, vas deferens, seminal vesicle, and ejaculatory duct. At 32-36 wk, the testis, which is anchored at the internal inguinal ring by the gubernaculum, begins its process of descent. The gubernaculum distends the inguinal canal and guides the testis into the scrotum. Following testicular descent, the patent processus vaginalis (hernia sac) normally involutes. A small percentage have Klinefelter syndrome or mutations in the insulin-like factor 3 receptor.

Clinical Manifestations
Undescended testes are classified as abdominal (nonpalpable), peeping (abdominal but can be pushed into the upper part of the inguinal canal), inguinal, gliding (can be pushed into the scrotum but retracts immediately to the pubic tubercle), and ectopic (superficial inguinal pouch or, rarely, perineal). Most undescended testes are palpable just distal to the inguinal canal over the pubic tubercle.

A disorder of sex development should be suspected in a newborn phenotypic male with bilateral nonpalpable testes, as the child could be a virilized girl with congenital adrenal hyperplasia (see Chapter 576). In a boy with midpenile or proximal hypospadias and a palpable undescended testis, disorder of sexual development is present in 15%, and the risk is 50% if the testis is nonpalpable.

The consequences of cryptorchidism include poor testicular growth, infertility, testicular malignancy, associated hernia, torsion of the cryptorchid testis, and the possible psychologic effects of an empty scrotum.

The undescended testis is normal at birth histologically, but pathologic changes can be demonstrated by 6-12 mo. Delayed germ cell maturation, reduction in germ cell number, hyalinization of the
Seminal tubules, and reduced Leydig cell number are typical; these changes are progressive over time if the testis remains undescended. Similar, although less severe, changes are found in the contralateral descended testis after 4-7 yr. After treatment for a unilateral undescended testis, 85% of patients are fertile, which is slightly less than the 90% rate of fertility in an unselected population of men. In contrast, following bilateral orchiopexy, only 50-65% of patients are fertile.

The risk of a germ cell malignancy (see Chapter 503) developing in an undescended testis is 4 times higher than in the general population, and is approximately 1 in 80 with a unilateral undescended testis and 1 in 40-50 for bilateral undescended testes. Testicular tumors are less common if the orchiopexy is performed before 10 yr of age, but they still occur, and adolescents should be instructed in testicular self-examination. The peak age for developing a testis tumor is 15-45 yr. The most common tumor developing in an undescended testis in an adolescent or adult is a seminoma (65%); after orchiopexy, nonseminomatous tumors represent only 65% of testis tumors. Orchiopexy reduces the risk of seminoma. Whether early orchiopexy reduces the risk of developing cancer of the testis is controversial, but it is uncommon for testis tumors to occur if the orchiopexy performed before the age of 2 yr. The contralateral scrotal testis is not at increased risk for malignancy.

An indirect inguinal hernia usually accompanies a congenital undescended testis but rarely is symptomatic. Torsion and infarction of the cryptorchid testis also are uncommon but can occur because of excessive mobility of undescended testes. Consequently, inguinal pain and/or swelling in a boy with an undescended testis should raise the suspicion of an incarcerated hernia or testicular torsion of the undescended testis.

"Acquired" or ascending undescended testes occurs when a boy has a descended testis at birth, but during childhood, usually between 4-10 yr of age, the testis does not remain in the scrotum. Such boys often have a history of a retractile testis. With testicular ascent, on physical examination the testis often can be manipulated into the scrotum, but there is obvious tension on the spermatic cord. This condition is speculated to result from incomplete involution of the processus vaginalis, restricting spermatic cord growth, resulting in the testis gradually moving out of its scrotal position during a boy's somatic growth.

Retractile testes may be misdiagnosed as undescended testes. Boys older than age 1 yr often have a brisk cremasteric reflex, and if the child is anxious or ticklish during scrotal examination, the testis may be difficult to manipulate into the scrotum. Boys should be examined with their legs in a relaxed frogleg position, and if the testis can be manipulated into the scrotum comfortably, it is probably retractile. It should be monitored every 6-12 mo with follow-up physical examinations, because it can become an acquired undescended testis. Overall, as many as one-third of boys with a retractile testes develop an acquired undescended testis, and boys younger than 7 yr of age at diagnosis of a retractile testes are at greatest risk. Although definitive data are not available, it is generally thought that boys with a retractile testes are not at increased risk for infertility or malignancy.

Approximately 10% of undescended testes are nonpalpable testis. Of these, 50% are viable testes in the abdomen or high in the inguinal canal, and 50% are atrophic or absent, almost always in the scrotum, secondary to spermatic cord torsion in utero (vanishing testis). If the nonpalpable testis is abdominal, it will not descend after 3 mo of age. Although sonography often is performed to try to identify whether the testis is present, it rarely changes clinical management, because the abdominal testis and atrophic testes are not identified on sonography. As part of the ABIM Choosing Wisely campaign, in 2012 the American Urological Association recommended that inguinal/scrotal sonography not be performed routinely in boys with a nonpalpable testis, because it rarely alters the surgical management. However, inguinal/scrotal sonography might be beneficial in obese boys with a nonpalpable testis; in this clinical setting, the undescended testis often is nonpalpable, and an inguinal/scrotal sonogram can be beneficial in surgical planning. CT scanning is relatively accurate in demonstrating the presence of the testis, but the radiation exposure is significant. MRI is even more accurate, but the disadvantage is that general anesthesia is necessary in most young children. None of these imaging studies are 100% accurate and in general do not add significantly to clinical decision making by the pediatric urologist or pediatric surgeon. Consequently, its routine use is discouraged.

On physical examination of the scrotum, the child should be entirely undressed, to help him relax. The examiner should examine the patient's scrotum and inguinal canal using their dominant hand. The nondominant hand is positioned over the pubic tubercle and is pushed inferiorly toward the scrotum. The examiner's dominant hand is used to try to palpate the testis. If the testis is nonpalpable, the "soap test" often is useful; soap is applied to the inguinal canal and the examiner's hand, significantly reducing friction and facilitating identification of an inguinal testis. In addition, pulling on the scrotum can pull a high inguinal testis into a palpable position. One soft sign that a testis is absent is contralateral testicular hypertrophy, but this finding is not 100% diagnostic.

Treatment

The congenital undescended testis should be treated surgically by 9-15 mo of age. With anesthesia by a pediatric anesthesiologist, surgical correction at 6 mo is appropriate, because spontaneous descent of the testis will not occur after 4 mo of age. Most testes can be brought down to the scrotum with an orchiopexy, which involves an inguinal incision, mobilization of the testis and spermatic cord, and correction of an indirect inguinal hernia. The procedure is typically performed on an outpatient basis and has a success rate of 98%. In some boys with a testis that is close to the scrotum, a prescrotal orchiopexy can be performed. In this procedure, the entire operation is performed through an incision along the edge of the scrotum. Often the associated inguinal hernia also can be corrected with this incision. Advantages of this approach over the inguinal approach include shorter operative time and less postoperative discomfort.

In boys with a nonpalpable testis, diagnostic laparoscopy is performed in most centers. This procedure allows safe and rapid assessment of whether the testis is intraabdominal. In most cases, orchiopexy of the intraabdominal testis located immediately inside the internal inguinal ring is successful, but orchectomy should be considered in more difficult cases or when the testis appears to be atrophic. A 2-stage orchiopexy sometimes is needed in boys with a high abdominal testis. Boys with abdominal testes are managed with laparoscopic techniques at many institutions. Testicular prostheses are available for older children and adolescents when the absence of the gonad in the scrotum might have an undesirable psychologic effect. The FDA has approved a saline testicular implant. Solid silicone "carving block" implants also are used (Fig. 545-1). Placement of testicular prostheses early in childhood is recommended for boys with anorchia (absence of both testes).

The American Urological Association released guidelines for the evaluation and treatment of boys with an undescended testis in 2014. Table 545-1 summarizes the primary statements.

**SCROTAL SWELLING**

Scrotal swelling may be acute or chronic and painful or painless. Abrupt onset of painful scrotal swelling necessitates prompt evaluation because some conditions, such as testicular torsion and incarcerated inguinal hernia, require emergency surgical management. Tables 545-2 and 545-3 show the differential diagnosis.

**Clinical Manifestations**

A detailed history is helpful in determining the cause of the swelling and includes onset of pain—with testicular torsion, the pain often is sudden in onset and may be associated with exercise or minor genital trauma; duration of pain; radiation of pain—inguinal discomfort is common with testicular torsion, inguinal hernia, or epididymitis, and associated flank pain can occur with passage of a ureteral calculus; previous episodes of similar pain, which are common in boys with intermittent testicular torsion or inguinal hernia; nausea and vomiting, which are associated with testicular torsion and inguinal hernia; and irritative urinary symptoms, such as dysuria, urgency, and frequency.
Table 545-1 American Urological Association Guidelines for Evaluation and Treatment of Boys with an Undescended Testis

**DIAGNOSIS**

<table>
<thead>
<tr>
<th>Primary care providers should palpate testes for quality and position at each recommended well-child visit. (Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by 6 mo (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. (Standard)</td>
</tr>
<tr>
<td>Providers should refer boys with the possibility of newly diagnosed (acquired) cryptorchidism after 6 mo. (Standard)</td>
</tr>
<tr>
<td>Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD). (Standard)</td>
</tr>
<tr>
<td>Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of boys with cryptorchidism before referral because these studies rarely assist in decision making. (Standard)</td>
</tr>
<tr>
<td>Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. (Recommendation)</td>
</tr>
<tr>
<td>In boys with retractile testes, providers should monitor the position of the testes at least annually to monitor for secondary ascent. (Standard)</td>
</tr>
</tbody>
</table>

**TREATMENT**

<table>
<thead>
<tr>
<th>Providers should not use hormonal therapy to induce testicular descent, since evidence shows low response rates and lack of evidence for long-term efficacy. (Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the absence of spontaneous testicular descent by 6 mo (corrected for gestational age), specialists should perform surgery within the next year. (Standard)</td>
</tr>
<tr>
<td>In prepubertal boys with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchiopexy should be performed. (Standard)</td>
</tr>
<tr>
<td>In boys with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a boy has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic tests, or postpubertal age. (Clinical Principle)</td>
</tr>
<tr>
<td>Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. (Clinical Principle)</td>
</tr>
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Table 545-2 Differential Diagnosis of Scrotal Masses in Boys and Adolescents

<table>
<thead>
<tr>
<th><strong>PAINFUL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular torsion</td>
</tr>
<tr>
<td>Torsion of appendix testis</td>
</tr>
<tr>
<td>Epididymitis</td>
</tr>
<tr>
<td>Trauma: ruptured testis, hematocoele</td>
</tr>
<tr>
<td>Inguinal hernia (incarcerated)</td>
</tr>
<tr>
<td>Mumps orchitis</td>
</tr>
<tr>
<td>Testicular vasculitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PAINLESS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocele</td>
</tr>
<tr>
<td>Inguinal hernia*</td>
</tr>
<tr>
<td>Varicocele*</td>
</tr>
<tr>
<td>Spermatocele*</td>
</tr>
<tr>
<td>Testicular tumor*</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura*</td>
</tr>
<tr>
<td>Idiopathic scrotal edema</td>
</tr>
</tbody>
</table>

*May be associated with discomfort.

Table 545-3 Differential Diagnosis of Scrotal Swelling in Newborn Boys

<table>
<thead>
<tr>
<th><strong>Hydrocele</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inguinal hernia (reducible)</td>
</tr>
<tr>
<td>Inguinal hernia (incarcerated)*</td>
</tr>
<tr>
<td>Torsion of appendix testis*</td>
</tr>
<tr>
<td>Scrotal hematoma</td>
</tr>
<tr>
<td>Testicular tumor</td>
</tr>
<tr>
<td>Meconium peritonitis</td>
</tr>
<tr>
<td>Epididymitis*</td>
</tr>
</tbody>
</table>

*May be associated with discomfort.

which indicate a urinary tract infection that can cause epididymitis. Some boys report a recent history of scrotal trauma. There are multiple reports of familial testicular torsion. Boys with lower urinary tract pathology such as urethral stricture or neuropathic bladder may be prone to epididymitis.

**Physical examination** may be difficult in boys with a painful scrotum. Some have advocated performing a spermatic cord block or administering intravenous analgesia to facilitate the examination, but such measures usually are unnecessary. Scrotal wall erythema is common in testicular torsion, epididymitis, torsion of the appendix testis, and an incarcerated hernia. In boys with a normal cremaster reflex, torsional torsion is unlikely. Absence of a cremasteric reflex is nondiagnostic.

**Laboratory Findings and Diagnosis**

Pertinent laboratory studies include a urinalysis and culture. A positive urinalysis suggests bacterial epididymitis. Serum studies are not helpful in establishing a diagnosis, unless a testicular malignancy is suspected. After initial evaluation, in boys with testicular pain color Doppler ultrasonography often is helpful in establishing the diagnosis, because it assesses whether testicular blood flow is normal, reduced, or increased (Fig. 545-2). If a hydrocele is present and the testis is nonpalpable, or if an abnormality of the testis is found, sonography also is indicated. Imaging studies are not 100% accurate; they should not be used to decide whether a boy with testicular pain should be referred for urologic evaluation.

Color Doppler ultrasonography allows assessment of testicular blood flow and testicular morphologic features. Accuracy is >95% if
the ultrasonographer is experienced and the patient is older than 2 yr old. A false-negative study (demonstrates normal testicular blood flow) can occur in a boy with testicular torsion if the degree of torsion is <360 degrees and the duration of torsion is short, because there may be continued testicular perfusion. In young boys, including neonates, blood flow may be difficult to demonstrate in 15% of normal testes.

TESTICULAR (SPERMATIC CORD) TORSION

Etiology

Testicular torsion requires prompt diagnosis and treatment to salvage the testis. Torsion is the most common cause of testicular pain in boys age 12 yr and older, and is uncommon before age 10 yr. It is caused by inadequate fixation of the testis within the scrotum, resulting from a redundant tunica vaginalis, allowing excessive mobility of the testis. The abnormal attachment is termed a bell clapper deformity and often is bilateral. Shortly after torsion occurs, venous congestion begins and subsequently arterial flow is interrupted. The likelihood of testis survival depends on the duration and severity of torsion. Following 4-6 hr of absent blood flow to the testis, irreversible loss of spermatogenesis can occur. Torsion may be familial in approximately 10% of males.

Diagnosis

Testicular torsion produces acute pain and swelling of the scrotum. On examination, the scrotum is swollen, and the testis is exquisitely tender and often difficult to examine. The cremasteric reflex nearly always is absent. The position (lie) of the testis is abnormal and there is often associated nausea and vomiting. The condition can be differentiated from an incarcerated hernia because swelling in the inguinal area typically is absent with torsion. If the pain duration is <4-6 hr, manual detorsion may be attempted. In 65% of cases the torsed testis rotates inward, so detorsion should be attempted in the opposite direction (e.g., the left testis is rotated clockwise). Successful manual detorsion results in dramatic pain relief.

Some adolescents experience intermittent testicular torsion. These boys report episodes of severe unilateral testicular pain that resolves spontaneously after 30-60 min. Treatment is elective bilateral scrotal orchiopexy (see Treatment).

Treatment

Treatment is prompt surgical exploration and detorsion. If the testis is explored within 6 hr of torsion, up to 90% of the gonads survive. Testicular salvage decreases rapidly with a delay of >6 hr. If the degree of torsion is 360 degrees or less, the testis might have sufficient arterial flow to allow the gonad to survive, even after 24-48 hr. Following detorsion the testis is fixed in the scrotum with nonabsorbable sutures, termed scrotal orchiopexy, to prevent torsion in the future. The contralateral testis also should be fixed in the scrotum because the predisposing anatomic condition often is bilateral. If the testis appears nonviable, orchiectomy is performed (Fig. 545-3A). Some adolescents do not undergo prompt evaluation and treatment and present with “late phase testicular torsion,” in which the spermatic cord contracts and the testis is high in the scrotum and nontender (Fig. 545-3B). Fertility is reduced in men who experience spermatic cord torsion in adolescence, irrespective of whether detorsion or orchiectomy is performed.

Spermatic cord torsion also can occur in the fetus or neonate. This condition results from incomplete attachment of the tunica vaginalis to the scrotal wall and is “extravaginal.” When torsion occurs in utero, the baby usually is born with a large, firm, nontender testis. Usually the ipsilateral hemiscrotum is ecchythmic (Fig. 545-4). In these cases, the testis rarely is viable because torsion was a remote event. However, the contralateral testis is at increased risk for torsion until 1-2 mo beyond term. The pediatric urology community is divided regarding whether immediate exploration is necessary in a male newborn who has suspected testicular torsion at birth, but if observation is recommended, the family needs to be counseled regarding the risk of contralateral spermatic cord torsion. On the other hand, if the initial exam is normal, and the newborn subsequently develops scrotal swelling and erythema, and imaging is consistent with spermatic cord torsion, emergency scrotal exploration is indicated.

TORSION OF THE APPENDIX TESTIS

Torsion of the appendix testis is the most common cause of testicular pain in boys 2-10 yr but is rare in adolescents. The appendix testis is a stalk-like structure that is a vestigial embryonic remnant of the Müllerian (paramesonephric) ductal system that is attached to the upper

Figure 545-2 Testicular torsion and axis change. A color Doppler ultrasound in the transverse plane shows color flow in the right testicle. The right testicle is oval to circular, because it has been evaluated in the transverse plane. The left testicle is elongated as if it is in longitudinal plane. This axis change is the ultrasound equivalent of the worrisome clinical finding suggestive of torsion when accompanied by a history of sudden pain. Lack of color Doppler flow in the left testicle confirms a left testicular torsion. (From Coley BD, editor: Caffey’s pediatric imaging, ed 12, Philadelphia, Elsevier, 2013, Fig. 126-13, p. 1300).

Figure 545-3 A, Left testicular torsion in adolescent with acute scrotum; the testis is necrotic. B, “Late-phase torsion” in an adolescent with severe testicular pain 1 mo previously. Note absence of inflammation and high position of testis in scrotum.
Part XXIV  Urologic Disorders in Infants and Children

EPIDIDYMITIS
Acute inflammation of the epididymis is an ascending retrograde infection from the urethra, through the vas into the epididymis. This condition causes acute scrotal pain, erythema, and swelling. It is rare before puberty and should raise the question of a congenital abnormality of the wolffian duct, such as an ectopic ureter entering the vas. In younger boys, the responsible organism is often *Escherichia coli* (see Chapter 200). After puberty, bacterial epididymitis becomes progressively more common and is the principal cause of acute painful scrotal swelling in young sexually active men. Urinalysis usually reveals pyuria. Epididymitis can be infectious (usually gonococcus or *Chlamydia*; see Chapters 192 and 226), but often the organism remains undetermined. Additional etiologies include familial Mediterranean fever, enterovirus, and adenoviruses. Treatment consists of bed rest and antibiotics as indicated. Differentiation from torsion can be difficult, and surgical exploration may be required in children.

Henoch-Schönlein purpura (see Chapter 484) is a systemic vasculitis that involves multiple organ systems and that can involve the kidney and spermatic cord. When the spermatic cord is involved, typically there is bilateral painful scrotal swelling with purpuric lesions involving the scrotum. Scrotal sonography should show normal testicular blood flow. Treatment is directed toward systemic treatment of the Henoch-Schönlein purpura. Isolated testicular vasculitis is less common than that in Henoch-Schönlein purpura; polyarteritis nodosa should be suspected.

VARICOCELE
A varicocele is a congenital condition in which there is abnormal dilation of the pampiniform plexus in the scrotum, often described as a “bag of worms” (Fig. 545-6). Dilation of the pampiniform venous plexus results from valvular incompetence of the internal spermatic vein. Approximately 15% of adult men have a varicocele; of these, approximately 10-15% are subfertile. Varicocele is the most common (and virtually the only) surgically correctable cause of subfertility in men. A varicocele is found in 5-15% of adolescent boys, but it rarely is diagnosed in boys younger than 10 yr old, because the varicocele becomes distended only after the increased blood flow associated with puberty occurs. Varicoceles occur predominantly on the left side, are bilateral in 2% of cases, and rarely involve the right side only. A varicocele in a boy younger than age 10 yr or on the right side might indicate an abdominal or retroperitoneal mass; an abdominal sonogram or CT scan should be performed in such cases.

A varicocele typically is a painless paratesticular mass. Occasionally patients describe a dull ache in the affected testis. Usually the varicocele is not apparent when the patient is supine because it is decompressed; in contrast, the varicocele becomes prominent when the patient is...
Disorders

HYDROCELE

Etiology

A hydrocele is an accumulation of fluid in the tunica vaginalis (Fig. 545-7). Between 1% and 2% of neonates have a hydrocele. In most cases, the hydrocele is noncommunicating (the processus vaginalis was obliterated during development). In such cases, the hydrocele fluid disappears by 1 yr of age. If there is a persistently patent processus, the hydrocele persists and becomes progressively larger during the day and is small in the morning. A rare variant of a hydrocele is the abdominocrotal hydrocele, in which there is a large, tense hydrocele that extends into the lower abdominal cavity. In some older boys, a noncommunicating hydrocele can result from an inflammatory condition within the scrotum, such as testicular torsion, torsion of the appendix testis, epididymitis, or testicular tumor. The long-term risk of a communicating hydrocele is the development of an inguinal hernia. Some older boys and adolescents also develop a hydrocele. In some cases hydrocele develop acutely after an episode of scrotal trauma or epididymoorchitis, whereas others develop more insidiously.

Diagnosis

On examination, hydroceles are smooth and nontender. Transillumination of the scrotum confirms the fluid-filled nature of the mass. It is important to palpate the testis, because some young men develop a hydrocele in association with a testis tumor. If compression of the fluid-filled mass completely reduces the hydrocele, an inguinal hernia/hydrocele is the likely diagnosis.

Treatment

Most congenital hydroceles resolve by 12 mo of age following reabsorption of the hydrocele fluid. If the hydrocele is large and tense, however, early surgical correction should be considered, because it is difficult to verify that the child does not have a hernia, and large hydroceles rarely disappear spontaneously. Hydroceles persisting beyond 12-18 mo usually are communicating and should be repaired. Surgical correction is similar to a herniorrhaphy (see Chapter 346). Through an inguinal incision, the spermatic cord is identified, the hydrocele fluid is drained, and a high ligation of the processus vaginalis is performed. If an older boy has a large hydrocele, often diagnostic laparoscopy can be performed to determine whether there is a patent processus vaginalis, and if the internal ring is closed, then the hydrocele may be corrected with a scrotal incision.

SPERMATOCELE

A spermatocele is a cystic lesion that contains sperm and is attached to the upper pole of the sexually mature testis. Spermatoceles usually are painless and are incidental findings on physical examination. Enlargement of the spermatocele or significant pain is an indication for removal.

TESTICULAR TUMOR

Testicular and paratesticular tumors can occur at any age, even in the newborn. Approximately 35% of prepubertal testis tumors are malignant; most commonly they are yolk sac tumors, although rhabdomyosarcoma and leukemia also can occur in this age group. In adolescents, 98% of painless solid testicular masses are malignant (see Chapter 503). Most manifest as a painless, hard testicular mass that does not transluminate. Scrotal ultrasonography should be performed to confirm the finding of a testicular mass and it can help to delineate the type of testis tumor. Serum tumor markers, including α-fetoprotein and β-human
chorionic gonadotropin, should be drawn. Definitive therapy includes surgical exploration through an inguinal incision. In most cases, a radical orchiectomy, consisting of removal of the entire testis and spermatic cord, is performed. In a prepubertal boy, if the ultrasonographic study or surgical exploration suggests that the tumor is localized and benign, such as a teratoma or epidermoid cyst, testis-sparing surgery with removal only of the mass may be appropriate.

Testicular microlithiasis identified incidentally with ultrasonography may be a risk factor for future neoplasia.

Bibliography is available at Expert Consult.
Bibliography
Chapter 546
Trauma to the Genitourinary Tract
Jack S. Elder

**ETIOLOGY**
Most injuries to the genitourinary tract in children result from blunt trauma during falls, athletic activities, or motor vehicle crashes (see Chapter 72). Children are at greater risk of blunt renal injury than are adults, because they have less body fat and because the kidneys are not located directly behind the ribs. Children with a preexisting renal anomaly, such as hydronephrosis secondary to a ureteropelvic junction obstruction, horseshoe kidney, or renal ectopia, also are at increased risk for renal injury. Blunt abdominal or flank trauma often causes a renal injury. Failing can cause a deceleration injury that results in an injury to the renal pedicle, interrupting blood flow to the kidney. If the bladder is full, blunt lower abdominal trauma can cause a bladder rupture. Rupture of the membranous urethra occurs in 5% of pelvic fractures. Straddle injuries usually are associated with trauma to the bulbous urethra.

Symptoms and signs of urinary tract injury include gross or microscopic hematuria, bleeding from the urethral meatus, abdominal or flank pain, a flank mass, fractured lower ribs or lumbar transverse processes, and a perineal or scrotal hematoma.

In more than 50% of cases there also are major injuries to the brain, spinal cord, skeleton, lungs, or abdominal organs.

**DIAGNOSIS**
Evaluation of the patient begins after an adequate airway has been established and the patient is hemodynamically stable (see Chapter 67). With significant abdominal injury, gross hematuria or >50 red blood cells per high-power field, or suspicion of renal injury (deceleration injury, flank pain or bruise), renal imaging is indicated. The bladder should be catheterized unless blood is dripping from the urethral meatus, which is an indication of potential urethral injury. Passing the catheter in the presence of a urethral injury can increase the extent of the damage and convert a partial membranous urethral tear into a total disruption. In these patients, a retrograde urethrogram should be performed by injecting radiopaque contrast medium into the urethral meatus under fluoroscopy. Oblique radiographs demonstrate the extent of the injury and whether urethral continuity is preserved or has been disrupted.

A 3-phase spiral CT scan should be performed to evaluate the kidneys, ureters, and bladder. The delayed images are important to detect renal extravasation of blood or urine. Prompt function of both kidneys without extravasation usually excludes significant renal injury. Renal injuries are classified according to the grading scale presented in Table 546-1. Minor renal injuries are most common; these include contusion of the renal parenchyma and shallow cortical lacerations not involving the collecting system. Major renal injuries include deep lacerations involving the collecting system, the shattered kidney, and renal pedicle injuries (Fig. 546-1). Complete absence of function of 1 kidney without contralateral compensatory hypertrophy (indicating congenital absence) should be regarded as an indication of major injury to the renal pedicle. Renal angiography, once used for further evaluation of renal injuries, particularly if a renal pedicle injury is suspected, now is rarely used because such patients are often hemodynamically unstable, and management is not significantly affected by the findings. In some cases, a preexisting renal anomaly is demonstrated on the study. A ruptured ureteropelvic junction obstruction may be apparent if the kidney is intact but the distal ureter is not visualized.

If there is a pelvic fracture, a urethral transection injury should be suspected. The risk is directly related to the number of broken pubic

---

**Table 546-1** Grading of Renal Injuries

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Renal contusion or subcapsular hematoma</td>
</tr>
<tr>
<td>2</td>
<td>Nonexpanding perirenal hematoma, &lt;1 cm parenchymal laceration, no urinary extravasation; all renal fragments viable; confined to renal retroperitoneum</td>
</tr>
<tr>
<td>3</td>
<td>Nonexpanding perirenal hematoma, &gt;1 cm parenchymal laceration, no urinary extravasation; renal fragments may be viable or devitalized</td>
</tr>
<tr>
<td>4</td>
<td>Laceration extending into the collecting system with urinary extravasation; renal fragments may be vital or devitalized, or Injury to the main renal vasculature with contained hemorrhage</td>
</tr>
<tr>
<td>5</td>
<td>Completely shattered kidney; by definition multiple major lacerations &gt;1 cm associated with multiple devitalized fragments, or Injury to the main renal vasculature with uncontrolled hemorrhage, renal hilar avulsion</td>
</tr>
</tbody>
</table>

---

**Figure 546-1** CT scan of a girl who sustained major renal injury when she fell off a bicycle. The scan demonstrates a ruptured right kidney with urinary extravasation.
rami and whether there is separation of the pubic symphysis or displacement of the posterior pubic arch. Radiographic evaluation with retrograde urethrogram should be performed if there is blood at the urethral or vaginal meatus, inability to void, and a perineal or penile hematoma.

TREATMENT
Minor renal injuries such as contusions are managed by bed rest and monitoring of vital signs until abdominal or flank discomfort and gross hematuria have resolved. Children with a major renal injury usually are admitted to an intensive care unit for continuous monitoring of vital signs and urine output. Intravenous antibiotics are also administered. These injuries also are managed nonoperatively, because Gerota's fascia often causes tamponade of bleeding from the kidney, and dramatic healing of the injured parenchyma can occur even with significant urinary extravasation.

Approximately 10% of children with a major renal injury undergo surgical exploration because of hemodynamic instability, persistent extravasation, or persistent hematuria or to correct a congenital renal deformity. It can be difficult to identify normal and devitalized parenchyma, and the likelihood of having to remove the kidney is significant. If the child is undergoing exploration for other abdominal injuries, the injured kidney is examined. If there is persistent extravasation because of intermittent ureteral obstruction from a blood clot, passage of a temporary double-J stent endoscopically between the bladder and kidney might allow resolution. If the renal pedicle is injured, nephrectomy is necessary. The kidney can be salvaged by emergency renal revascularization only if the kidney is explored within 2-3 hr of the injury. Virtually all penetrating injuries of the kidneys should be explored.

In addition to loss of renal function, the main long-term complication of renal injury is renin-mediated hypertension. Children who sustain significant renal injuries should have periodic measurement of blood pressure if they have any residual renal abnormality.

Urinary injuries usually are iatrogenic. Injuries of the ureter by blunt or penetrating trauma require immediate surgical attention.

When the bladder can be catheterized, a static cystogram is obtained, infusing a contrast solution through the catheter by gravity, ideally using fluoroscopy. Flat and oblique views are often obtained; a postvoid film also should be obtained because, in some cases, extravasation may be hidden by the full bladder.

Bladder ruptures can be intraperitoneal or extraperitoneal. All intraperitoneal ruptures require surgical repair. Minor extraperitoneal near-ruptures might be treated by catheter drainage but generally require surgical treatment.

Treatment of a membranous urethral injury is controversial. Erectile dysfunction, urethral stricture, and urinary incontinence are the major late complications of rupture of the membranous urethra, and therapy is directed at minimizing the risk of these problems. A large pelvic hematoma with tamponade is often present, and an immediate attempt to repair the injury can be technically difficult and result in significant hemorrhage. Many such injuries are managed initially by temporary suprapubic cystostomy, with continuous bladder drainage for 3-6 mo. Subsequently, open or endoscopic urethroplasty can be performed. Alternatively, some try to achieve urethral continuity under anesthesia and leave a urethral catheter for several months. These patients typically require subsequent open urethroplasty.

Penile injury is uncommon. A risk of newborn circumcision with a Mogen clamp is partial or complete glans amputation. With immediate surgical repair, often the excised glans tissue can be replaced as a free graft. Some boys who are in the process of toilet training sustain an injury to the glans penis if the lid of the toilet falls while they are urinating. These boys often have a hematoma covering the distal half of the glans. Typically, they have no difficulty urinating and do not need extensive evaluation. Some male infants develop an inadvertent hair coil tourniquet or strangulation injury. Typically a very narrow constriction is noted with severe distal penile swelling and pain. Identification and incision of the hair allows prompt resolution of the edema. The urethra and penile vascularity should be assessed after release of the hair coil. Adolescent boys who indulge in extremely vigorous sexual intercourse may sustain rupture of one of the corporal bodies. These boys have severe swelling of the penile shaft and require emergency exploration and repair. Boys with penetrating injuries of the penis also require emergency debridement and repair.

Testicular injuries are relatively uncommon in children because of the small size of the testes and their mobility within the scrotum. Such injuries usually result from blunt trauma during athletic activity. Typically, these boys have significant scrotal swelling, testicular pain, and tenderness (Fig. 546-2A). Ultrasonography demonstrates rupture of the tunica albuginea, which is the capsule of the testis, and surrounding hemorrhage. Prompt surgical treatment of testicular injuries increases the salvage rate (Fig. 546-2B). An uncommon injury is the zipper injury, which can affect either the scrotum or foreskin. This problem generally occurs in boys who do not wear underwear. The zipper can be cut with bone cutters or metal cutters. Sedation generally is unnecessary.

Bibliography is available at Expert Consult.
Bibliography
Urolithiasis is less common in the United States than in other parts of the world. Approximately 7% of urinary calculi occur in children younger than 16 yr of age. In the United States, many children with stone disease have a metabolic abnormality. The exceptions are patients with a neurogenic bladder (see Chapter 542), who are prone to infection-initiated renal stones, and those who have urinary tract reconstruction with small or large intestine, which predisposes to bladder calculi. The incidence of metabolic stones is similar in boys and girls; they are most common in southeastern United States and are uncommon in African-Americans. In Southeast Asia, urinary calculi are endemic and are related to dietary factors. Contamination of infant formula with the organic base and illegally added nitrogen-containing food additive melamine was reported in China in 2008 and is the source of much study in that country.

STONE FORMATION

Nearly 90% of urinary stones contain calcium as a major constituent, and 60% are composed of calcium oxalate. Most “spontaneous” stones are composed of calcium, oxalate, or phosphate crystals; others are caused by uric acid, cystine, ammonium crystals, or phosphate crystals, or a combination of these substances (Table 547-1). The risk of stone formation increases in the presence of increasing concentrations of these crystals and is reduced with increasing concentrations of urinary inhibitors. Renal calculi develop from crystals that form on the calyx and aggregate to form a calculus. Bladder calculi may be stones that formed in the kidney and traveled down the ureter, or they can form primarily in the bladder.

Low urine volume, low urine pH, calcium, sodium, oxalate, and urate are known to promote stone formation. Many inorganic (e.g., citrate, magnesium) and organic (e.g., glycosaminoglycans, osteopontin) substances are known to inhibit stone formation. Organic inhibitory compounds adsorb to the surface of the crystal, thereby inhibiting crystal growth and nucleation.

Stone formation depends on 4 factors: matrix, precipitation-crystallization, epitaxy, and the absence of inhibitors of stone formation in the urine. Matrix is a mixture of protein, nonamino sugars, glucosamine, water, and organic ash that makes up 2-9% of the dry weight of urinary stones and is arranged within the stones in organized concentric laminations. Precipitation-crystallization refers to supersaturation of the urine with specific ions forming the crystal. Crystals aggregate by chemical and electrical forces. Increasing the saturation of urine with respect to the ions increases the rate of nucleation, crystal growth, and aggregation and increases the likelihood of stone formation and growth. Epitaxy refers to the aggregation of crystals of different composition but similar lattice structure, thus forming stones of a heterogeneous nature. The lattice structures of calcium oxalate and monosodium urate have similar structures, and calcium oxalate crystals can aggregate on a nucleus of monosodium urate crystals. Urine also contains inhibitors of stone formation, including citrate, diphosphonate, and magnesium ion.

| Table 547-1 |
| Classification of Urolithiasis |
| **CALCITRIS STONES (CALCITRIS OXALATE AND CALCIUM PHOSPHATE)** |
| Hypercalcuvria |
| Absorptive: increased Ca absorption from gut; types I and II |
| Renal leak: increased tubular reabsorption of Ca |
| Resorptive |
| Primary hyperparathyroidism (rare in children) |
| Iatrogenic |
| Loop diuretics |
| Ketogenic diet |
| Corticosteroids |
| Adrenocorticotropic hormone administration |
| Methylxanthines (theophylline, aminophylline) |
| Distal renal tubular acidosis, type 1 (calcium phosphate) |
| Hypocitraturia—citrate most important inhibitor of Ca crystallization |
| Vitamin D excess |
| Immobilization |
| Sarcoidosis |
| Cushing disease |
| Hyperuricuria |
| Heterozygous cystinuria |
| Hyperoxaluria (calcium oxalate) |
| Primary hyperoxaluria, types 1 and 2 |
| Secondary hyperoxaluria |
| Enteric hyperoxaluria |

**CYSTINE STONES**

Cystinuria

**STRUVITE STONES (MAGNESIUM AMMONIUM PHOSPHATE)**

Urinary tract infection (urea-splitting organism)

Foreign body

Urinary stasis

**URIC ACID STONES**

Hyperuricuria

Lesch-Nyhan syndrome

Myeloproliferative disorders

After chemotherapy

Inflammatory bowel disease

**INDINAVIR STONES**

**MELANIN**

**NEPHROCALCINOSIS**

*Most common.

**CLINICAL MANIFESTATIONS**

Children with urolithiasis usually have gross or microscopic hematuria. If the calculus causes obstruction, then severe flank pain (renal colic) or abdominal pain occurs. The calculus typically causes obstruction at areas of narrowing of the urinary tract—the ureteropelvic junction, where the ureter crosses the iliac vessels, and the ureterovesical junction. The ureter progressively narrows distally, and its most narrow segment is the ureterovesical junction. Typically the pain radiates anteriorly to the scrotum or labia. Often the pain is intermittent, corresponding to periods of obstruction of urine flow, which increases the pressure in the collecting system. If the calculus is in the distal ureter, the child can have irritable symptoms of dysuria, urgency, and frequency. If the stone passes into the bladder, the child usually is asymptomatic. If the stone is in the urethra, dysuria and difficulty voiding can result, particularly in boys. Some children pass small amounts of gravel-like material. Stones can also be asymptomatic, although it is uncommon to pass a ureteral calculus without symptoms.

**DIAGNOSIS**

Approximately 90% of urinary calculi are calcified to some degree and consequently are radiopaque on a plain abdominal film. However, many calculi are only a few millimeters in diameter and are difficult to
Laboratory Tests Suggested for Evaluation of Urolithiasis

<table>
<thead>
<tr>
<th>SERUM</th>
<th>URINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Urine culture</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Calcium: creatinine ratio</td>
</tr>
<tr>
<td>Electrolytes and anion gap</td>
<td>Spot test for cystinuria</td>
</tr>
<tr>
<td>Creatinine</td>
<td>24 hr collection for:</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Creatinine clearance</td>
</tr>
</tbody>
</table>

Table 547-2

PATHOGENESIS OF SPECIFIC RENAL CALCULI

**Calcium Oxalate and Calcium Phosphate Calculi**

Most urinary calculi in children in the United States are composed of calcium oxalate and/or calcium phosphate. The most common metabolic abnormality in these patients is normocalcemic hypercalciuria. Between 30% and 60% of children with calcium stones have hypercalciuria without hypercalcemia. Other metabolic aberrations that predispose to stone disease include hyperoxaluria, hyperuricosuria, hypocitruria, heterozygous cystinuria, hypomagnesuria, hyperparathyroidism, and renal tubular acidosis (see Chapter 529).

**Hypercalciuria** may be absorptive, renal, or resorptive. The primary disturbance in absorptive hypercalciuria is intestinal hyperabsorption of calcium. In some children, an increase in 1,25-dihydroxyvitamin D is associated with the increased calcium absorption, whereas in others the involvement is independent of vitamin D. Renal hypercalciuria refers to impaired renal tubular reabsorption of calcium (see Chapter 519.8). Renal leak of calcium causes mild hypocalcemia, which triggers an increased production of parathyroid hormone, with increased intestinal absorption of calcium and increased mobilization of calcium stores. Resorptive hypercalciuria is uncommon and is found in patients with primary hyperparathyroidism. Excess parathyroid hormone secretion stimulates intestinal absorption of calcium and mobilization of calcium stores. Table 547-4 summarizes the metabolic evaluation of children with hypercalciuria.

**Hyperoxaluria** is another potentially important cause of calcium stones. Oxalate increases the solubility product of calcium oxalate crystallization 7-10 times more than calcium. Consequently, hyperoxaluria significantly increases the likelihood of calcium oxalate precipitation. Oxalate is found in high concentration in tea, coffee, spinach, and rhubarb. Primary hyperoxaluria is a rare autosomal recessive disorder that can be subclassified into glycolic aciduria and L-glyceric aciduria. Most patients with primary hyperoxaluria have glycolic aciduria; oxalic and glycolic acids are increased in the urine of affected persons. Both defects cause increased endogenous production of oxalate, with hyperoxaluria, urolithiasis, nephrocalcinosis, and injury to the kidneys. Death from renal failure occurs by age 20 yr in untreated patients. Oxalosis, defined as extrarenal deposition of calcium oxalate, occurs when renal insufficiency is present with elevated plasma oxalate. Calcium oxalate deposits appear first in blood vessels and bone marrow, and with time they appear throughout the body. Secondary hyperoxaluria is more common and can occur in patients with increased intake of oxalate and oxalate precursors such as vitamin C, in those with pyridoxine deficiency, and in children with intestinal malabsorption.

**Enteric hyperoxaluria** refers to disorders such as inflammatory bowel disease (see Chapter 336), pancreatic insufficiency (see Chapter 350), and biliary disease (see Chapter 356), in which there is gastrointestinal malabsorption of fatty acids, which bind intraluminal calcium and form salts that are excreted in the feces. Normally, calcium forms a complex with oxalate to reduce oxalate absorption, but if calcium is unavailable, there is increased absorption of unbound oxalate.
Hypocitraturia refers to a low excretion of citrate, which is an important inhibitor of calcium stone formation. Citrate acts as an inhibitor of calcium urolithiasis by forming complexes with calcium, increasing the solubility of calcium in the urine, and inhibiting the aggregation of calcium phosphate and calcium oxalate crystals. Disorders such as chronic diarrhea, intestinal malabsorption, and renal tubular acidosis (see below) can cause hypocitraturia. It may also be idiopathic.

Renal tubular acidosis (RTA) is a syndrome involving a disturbance of acid–base balance within the kidney that can be classified into 3 types, one of which predisposes to renal calculi that typically are calcium phosphate (see Chapter 529). In type 1 RTA, the distal nephron does not secrete hydrogen ion into the distal tubule. The urine pH is never <5.8, and hyperchloremic hypokalemic acidosis results. Patients acquire nephrolithiasis, nephrocalcinosis, muscle weakness, and osteomalacia. Type 1 RTA can be an autosomal dominant disorder, but more often it is acquired and associated with systemic diseases such as Sjögren syndrome, Wilson disease, primary biliary cirrhosis, and lymphocytic thyroiditis, or it results from amphotericin B, lithium, or toluene (an organic solvent associated with glue sniffing).

From 5-8% of patients with cystic fibrosis (see Chapter 403) have urolithiasis. Typically the stones are calcium, and they often become manifest in adolescence or young adulthood. Microscopic nephrocalcinosis also occurs in younger children with the disease. These patients do not have hypercitraturia, and the propensity for urolithiasis has been speculated to result from an inability to excrete a sodium chloride load or from intestinal malabsorption.

Other disorders can play a role in causing calcium stones. Hyperuricosuria may be related to the epitaxial growth of calcium oxalate crystals around a nucleus of uric acid crystals or to the action of uric acid as a counter inhibitor of urinary mucopolysaccharides, which inhibit calcium oxalate crystallization. Heterozygous cystinuria is found in some patients with calcium stones. The mechanism is unknown but may be similar to that of uric acid. Sarcoidosis (see Chapter 165) causes an increased sensitivity to vitamin D₃ and thus an increased absorption of calcium from the gastrointestinal tract. In Lesch-Nyhan syndrome (see Chapter 89), there is excessive uric acid synthesis. These patients are more likely to form uric acid stones, but some of these stones may be calcified. Immobility can cause hypercalciuria by mobilization of calcium stores. High-dose corticosteroids can cause hypercalciuria and calcium oxalate precipitation. Furosemide, which is administered in the neonatal intensive care unit, also can cause severe hypercalciuria, urolithiasis, and nephrocalcinosis.

In some children, calcium calculi are idiopathic. A complete metabolic evaluation must be performed before this diagnosis is made.

**Cystine Calculi**

Cystinuria accounts for 1% of renal calculi in children. The condition is a rare autosomal recessive disorder of the epithelial cells of the renal tubule that prevents absorption of the 4 dibasic amino acids (cystine, ornithine, arginine, lysine) and results in excessive urinary excretion of these products. The only known complication of this familial disease is the formation of calculi, because of the low solubility of cystine. The patients usually have acidic urine, which leads to a higher rate of
of indinavir-based monohydrate, although calcium oxalate and/or phosphate have been present in some. After each dose, 12% of the drug is excreted unchanged in the urine. The urine in these patients often contains crystals of characteristic rectangles and fan-shaped or starburst crystals. Indinavir is soluble at a pH of <5.5. Consequently, dissolution therapy by urinary acidification with ammonium chloride or ascorbic acid should be considered.

**Nephrocalcinosis**

Nephrocalcinosis refers to calcium deposition within the renal tissue. Often nephrocalcinosis is associated with urolithiasis. The most common causes are furosemide (administered to premature neonates), distal RTA, hyperparathyroidism, medullary sponge kidney, hypophosphatemic rickets, sarcoidosis, cortical necrosis, hyperoxaluria, prolonged immobilization, Cushing syndrome, hyperuricosuria, monogenetic causes of hypertension, and renal candidiasis.

**TREATMENT**

In a child with a renal or ureteral calculus, the decision whether to remove the stone depends on its location, size, and composition (if known) and whether obstruction and/or infection is present. Pain is managed with nonsteroidal antiinflammatory drugs or opiates. Small ureteral calculi often pass spontaneously, although the child might experience severe renal colic. The narrowest segment of the ureter is the ureterovesical junction. α-Adrenergic blockers, such as tamsulosin, terazosin, and doxazosin, facilitate stone passage in children and adults by decreasing ureteral pressure below the stone and decreasing the frequency of the peristaltic contractions of the obstructed ureter. In many cases, passage of a ureteral stent past the stone endoscopically relieves pain and dilates the ureter sufficiently to allow the calculus to pass. In cases such as children with a uric acid calculus or an infant with a furosemide-associated calculus, dissolution alkaline therapy may be effective.

If the calculus does not pass or seems unlikely to pass or if there is associated urinary tract infection, removal is necessary (Table 547-5).

**Lithotripsy** of bladder, ureteral, and small renal pelvic calculi using the holmium laser through a flexible or rigid ureteroscope is quite effective. Extracorporeal shock wave lithotripsy has been successfully applied to children with renal and ureteral stones, with a success rate of >75%. Another alternative is percutaneous nephrolithotomy, in which access to the renal collecting system is obtained percutaneously, and the calculus are broken down by ultrasonic lithotripsy. In cases in which these modalities are unsuccessful, an alternative is laparoscopic removal; this procedure can be performed using the da Vinci robot.

In children with urolithiasis, the underlying metabolic disorder should be addressed (Table 547-6). Because lithiasis results from elevated concentrations of specific substances in the urine, maintaining a continuous high urine output by maintaining a high fluid intake often is an effective method of preventing further stones. The high fluid intake should be continued at night, and usually it is necessary for the child to get up at least once at night to urinate and drink more water.

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**Table 547-5 Primary Surgical Treatment Options vs Stone Size and Location**

<table>
<thead>
<tr>
<th>STONES</th>
<th>SHOCK WAVE LITHOTRIPSY</th>
<th>URETEROSCOPY</th>
<th>PERCUTANEOUS NEPHROLITHOTOMY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RENAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>Most common</td>
<td>Optional</td>
<td>Optional</td>
</tr>
<tr>
<td>1-2 cm</td>
<td>Most common</td>
<td>Optional</td>
<td>Optional</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>Noncommon</td>
<td>Rare</td>
<td>Most common</td>
</tr>
<tr>
<td><strong>LOWER POLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>Most common</td>
<td>Optional</td>
<td>Optional</td>
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<tr>
<td>&gt;1 cm</td>
<td>Optional</td>
<td>Optional</td>
<td>Most common</td>
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<tr>
<td><strong>URETERAL</strong></td>
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<tr>
<td>Proximal</td>
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<td>Most common</td>
</tr>
<tr>
<td>Distal</td>
<td>Optional</td>
<td>Optional</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Calcium and limited amounts of sodium and animal protein. Low-  
sodium, low-protein diets reduce urinary calcium and oxalate excretion. Children with stone disease should avoid excess calcium intake. However, children require calcium for bone development and recommendations for daily calcium intake vary by age. Consequently, calcium restriction in children should be avoided. Thiazide diuretics also reduce renal calcium excretion. Addition of potassium citrate, an inhibitor of calcium stones, with a dosage of 1-2 mEq/kg/24 hr is beneficial. An excellent source of citrate is lemonade, because 4 oz of lemon juice contains 84 mEq of citric acid. A daily mixture of 4 oz of reconstituted lemon juice in 2 L of water and sweetened to taste should significantly increase the urinary citrate level. In difficult cases, neutral orthophosphate should be given also, although it is poorly tolerated.

In patients with uric acid stones, allopurinol is effective. Allopurinol is an inhibitor of xanthine oxidase and is effective in reducing the production of both uric acid and 2,8-dihydroxyadenine and can help control recurrence of both types of stones. In addition, urinary alkalinization with sodium bicarbonate or sodium citrate is beneficial. The urine pH should be ≥6.5 and can be monitored at home by the family. Maintaining a high urine pH can also prevent recurrence of cystine calculi. Cystine is much more soluble when the urinary pH is >7.5, and alkalinization of urine with sodium bicarbonate or sodium citrate is beneficial. The urine pH should be ≥6.5 and can be monitored at home by the family.

A daily fluid intake of 2-2.5 L in adolescent stone formers is recommended, with greater intake during summer months.

Dietary sodium intake in children has increased significantly, up to 6.8 g/day as a consequence of increased consumption of salty, processed foods. High sodium intake increases urinary excretion of calcium and may result in hypocitraturia. In addition, increased salt intake induces metabolic acidosis. To compensate for the acid load, the kidneys conserve anions, including urinary citrate, which contributes to hypocitraturia. Reduction in dietary intake of sodium and increased potassium intake is indicated.

Although counterintuitive, low-calcium diets are less effective in the treatment of calcium stones than diets containing normal amounts of calcium and limited amounts of sodium and animal protein. Low-sodium, low-protein diets reduce urinary calcium and oxalate excretion. Children with stone disease should avoid excess calcium intake. However, children require calcium for bone development and recommendations for daily calcium intake vary by age. Consequently, calcium restriction in children should be avoided. Thiazide diuretics also reduce renal calcium excretion. Addition of potassium citrate, an inhibitor of calcium stones, with a dosage of 1-2 mEq/kg/24 hr is beneficial. An excellent source of citrate is lemonade, because 4 oz of lemon juice contains 84 mEq of citric acid. A daily mixture of 4 oz of reconstituted lemon juice in 2 L of water and sweetened to taste should significantly increase the urinary citrate level. In difficult cases, neutral orthophosphate should be given also, although it is poorly tolerated.

In patients with uric acid stones, allopurinol is effective. Allopurinol is an inhibitor of xanthine oxidase and is effective in reducing the production of both uric acid and 2,8-dihydroxyadenine and can help control recurrence of both types of stones. In addition, urinary alkalinization with sodium bicarbonate or sodium citrate is beneficial. The urine pH should be ≥6.5 and can be monitored at home by the family. Maintaining a high urine pH can also prevent recurrence of cystine calculi. Cystine is much more soluble when the urinary pH is >7.5, and alkalinization of urine with sodium bicarbonate or sodium citrate is beneficial. The urine pH should be ≥6.5 and can be monitored at home by the family.

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Table 547-6: Suggested Therapy for Urolithiasis Caused by Metabolic Abnormalities

<table>
<thead>
<tr>
<th>METABOLIC ABNORMALITY</th>
<th>INITIAL TREATMENT</th>
<th>SECOND-LINE TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>Reduction of dietary Na+</td>
<td>Potassium citrate</td>
</tr>
<tr>
<td></td>
<td>Dietary calcium at RDA</td>
<td>Neutral phosphate</td>
</tr>
<tr>
<td></td>
<td>Thiazides</td>
<td></td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td>Adjustment of dietary oxalate</td>
<td>Neutral phosphate*</td>
</tr>
<tr>
<td></td>
<td>Potassium citrate</td>
<td>Magnesium Pyridoxine*</td>
</tr>
<tr>
<td>Hypocitric aciduria</td>
<td>Potassium citrate Bicarbonate</td>
<td></td>
</tr>
<tr>
<td>Hyperuricosuria</td>
<td>Alkalization</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Cystinuria</td>
<td>Alkalization</td>
<td>Tiopronin (Thiola) D-Penicillamine</td>
</tr>
<tr>
<td></td>
<td>Reduction of dietary Na+</td>
<td></td>
</tr>
</tbody>
</table>

*Initial therapy in primary hyperoxaluria.

RDA, recommended dietary allowance.


Bibliography is available at Expert Consult.
Bibliography