

Section 1

Development and Function

Chapter 421

Diagnostic Approach to Respiratory Disease

Daniel J. Lesser, Julie Ryu,
Kelan G. Tantisira, and Gabriel G. Haddad

HISTORY

The history of the illness begins with a narrative provided by the parent/caretaker with input from the patient when possible. It should include questions about respiratory symptoms (dyspnea, cough, pain, wheezing, snoring, apnea, cyanosis, exercise intolerance), as well as their chronicity, timing during day or night, and associations with environmental exposures and 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 79.1 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 first few weeks of life and usually <60 breaths/min in the first 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. The FRC is the amount of air left in the lungs after tidal expiration. Children with obstructive disease might take slower, deeper breaths. When the obstruction is **extrathoracic** (from the nose to the mid-trachea), inspiration is more prolonged than expiration, and an inspiratory stridor (a predominant inspiratory monophonic noise) can

usually be heard (Fig. 421.1). 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 along with a possible increase in FRC (Fig. 421.2).

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 (pleural effusion, pneumonia, atelectasis), but it is tympanic 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**; **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 421.1). **Digital clubbing** is a sign of chronic hypoxia and chronic lung disease (Fig. 421.3) but may be a result of nonpulmonary etiologies (Table 421.2).

BLOOD GAS ANALYSIS

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 has 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, so in 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 a 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 (PIO_2)** at sea level is therefore $(760 - 47) \times 20.93\% = 149$ torr. When breathing 40% oxygen at sea level, PIO_2 is $(760 - 47) \times 40\% = 285$ torr. At higher altitudes, breathing different concentrations of oxygen, PIO_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), PIO_2 in room air is $(632 - 47) \times 20.93\% = 122$ torr, and in 40% oxygen, it is $(632 - 47) \times 40\% = 234$ torr.

Minute volume is a product of V_T and respiratory rate. Part of the V_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 $(V_T - \text{dead space}) \times \text{respiratory rate}$. Alveolar ventilation is inversely proportional to arterial PCO_2 (PaCO_2). When alveolar ventilation is halved, PaCO_2 is doubled. Conversely, doubling of alveolar ventilation decreases PaCO_2 by 50%. **Alveolar PO_2 (PaO_2)** is calculated by the **alveolar air equation** as follows, where R is the respiratory quotient. For practical purposes, PACO_2 is substituted by **arterial PCO_2 (PaCO_2)**, and R is assumed to be 0.8. According to the alveolar air equation, for a given PIO_2 , a rise in PaCO_2 of 10 torr results in a decrease in PAO_2 by $10 \div 0.8$, or 10×1.25 , or 12.5 torr. Thus proportionately inverse changes in PAO_2 occur to the extent of 1.25 times the changes in PACO_2 (or PaCO_2).

After the alveolar gas composition is determined by the inspired gas conditions and the 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

Fig. 421.1 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 with 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 the extrathoracic airway and amelioration of symptoms. (Courtesy Dr. Ashok Sarnaik.)

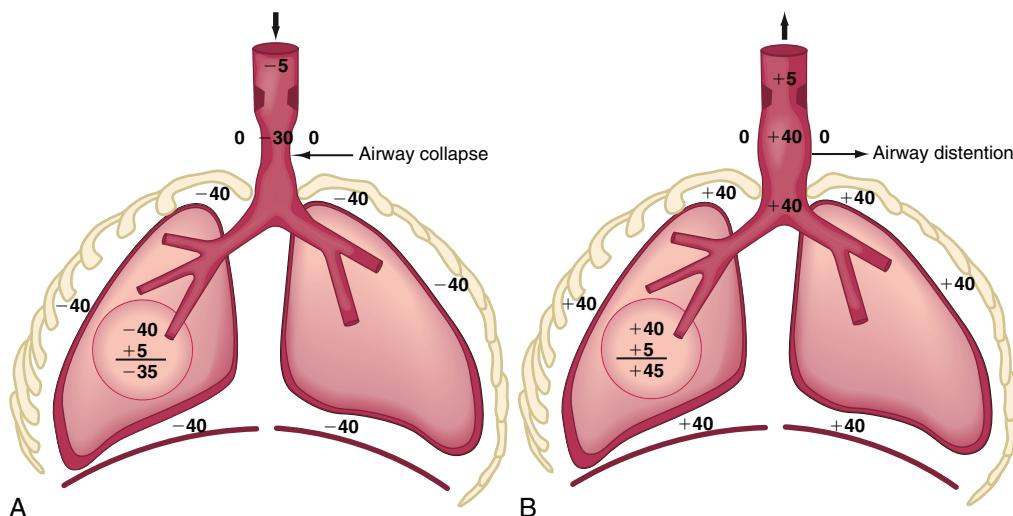


Fig. 421.2 A and B, In intrapulmonary airway obstruction, an even wider segment of intrathoracic airway is subjected to pressure changes compared with those observed in intrathoracic-extrapulmonary airway obstruction. Such lesions are associated with marked increase in airway obstruction during expiration. (Courtesy Dr. Ashok Sarnaik.)

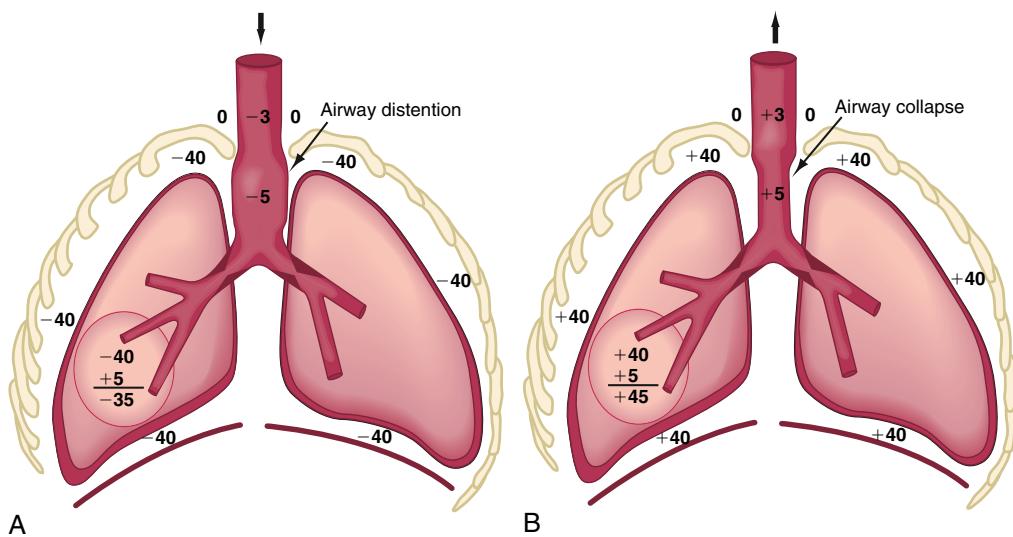


Table 421.1 Respiratory Sounds

BASIC SOUNDS	MECHANISMS	ORIGIN	ACOUSTICS	RELEVANCE
Lung	Turbulent flow, vortices, other	Central (expiration), lobar to segmental airways (inspiration)	Low-pass filtered noise (<100 to >1,000 Hz)	Regional ventilation, airway caliber
Tracheal	Turbulent flow, flow impinging on airway walls	Pharynx, larynx, trachea, large airways	Noise with resonances (<100 to >3,000 Hz)	Upper airway configuration
ADVENTITIOUS SOUNDS				
Wheezes	Airway wall flutter, vortex shedding, other	Central and lower airways	Sinusoidal (<100 to >1,000 Hz, duration typically >80 msec)	Airway obstruction, flow limitation
Rhonchi	Rupture of fluid films, airway wall vibration	Larger airways	Series of rapidly damped sinusoids (typically <300 Hz and duration <100 msec)	Secretions, abnormal airway collapsibility
Crackles	Airway wall stress-relaxation	Central and lower airways	Rapidly damped wave deflections (duration typically <20 msec)	Distal airway and alveolar closure, secretions

Modified from Pasterkamp H, Kraman SS, Wodicka GR. Respiratory sounds. Advances beyond the stethoscope. Am J Respir Crit Care Med. 1997;156(3):974–987.

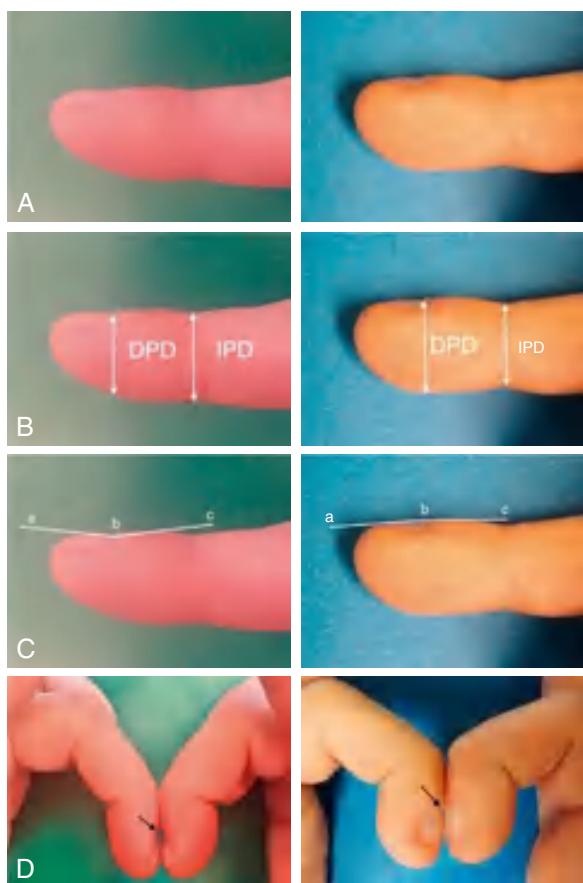


Fig. 421.3 A, Normal and clubbed finger viewed in profile. B, The normal finger demonstrates a distal phalangeal finger depth (DPD)/interphalangeal finger depth (IPD) ratio <1. The clubbed finger demonstrates a DPD/IPD ratio >1. C, The normal finger on the left demonstrates a normal profile (abc) with an angle less than 180 degrees. The clubbed finger demonstrates a profile angle >180 degrees. D, Schamroth sign is demonstrated in the clubbed finger with the loss of the diamond-shaped window in between finger beds (arrow) that is demonstrated in the normal finger. (From Wilmott RW, Deterding RR, Li A, et al, eds. *Kendig's Disorders of the Respiratory Tract in Children*, 9th ed. Philadelphia: Elsevier; 2019: Fig. 1.14, p. 20.)

equilibration of alveolar gas and pulmonary capillary blood is complete for both oxygen and carbon dioxide. In diseases in which the 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-aO₂) gradients** and hypoxemia. Significant elevation of CO₂ 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 Po₂ and Pco₂ 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 and venous admixture in a normal lung. Dead space ventilation results in a higher PaCO₂ than PACO₂, whereas venous admixture or right-to-left shunting results in a lower PaO₂ compared with the alveolar gas composition (Fig. 421.4). PaO₂ 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 Po₂, there is 0.3 mL of dissolved O₂ in 100 mL of blood. The total blood oxygen content is composed of the dissolved oxygen and the oxygen bound to hemoglobin (Hb). Each gram of Hb carries 1.34 mL of O₂ when

Table 421.2 Nonpulmonary Diseases Associated with Clubbing

CARDIAC

Cyanotic congenital heart disease
Bacterial endocarditis
Chronic heart failure

HEMATOLOGIC

Thalassemia
Congenital methemoglobinemia (rare)

GASTROINTESTINAL

Crohn disease
Ulcerative colitis
Celiac disease
Chronic dysentery, sprue
Polyposis coli
Severe gastrointestinal hemorrhage
Small bowel lymphoma
Liver cirrhosis (including α1-antitrypsin deficiency)
Chronic active hepatitis

OTHER

Thyroid deficiency (thyroid acropachy)
Thyrotoxicosis
Chronic pyelonephritis (rare)
Toxic (e.g., arsenic, mercury, beryllium)
Lymphomatoid granulomatosis
Fabry disease
Raynaud disease, scleroderma
Hodgkin disease
Familial

UNILATERAL CLUBBING

Vascular disorders (e.g., subclavian arterial aneurysm, brachial arteriovenous fistula)
Subluxation of shoulder
Median nerve injury
Local trauma

From Pasterkamp H. The history and physical examination. In: Wilmott RW, Boat TF, Bush A, et al, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*, 8th ed. Philadelphia: Elsevier; 2012.

100% saturated with oxygen. Thus 15 g of Hb carry 20.1 mL of oxygen. **Arterial oxygen content (CaO₂)**, expressed as mL O₂/dL blood, can be calculated as (PaO₂ × 0.003) + (Hb × 1.34 × So₂), where Hb is grams of Hb per deciliter of blood and So₂ is the percentage of oxyhemoglobin saturation. The relationship of Po₂ and the amount of oxygen carried by the Hb is the basis of the O₂-Hb dissociation curve (Fig. 421.5). The Po₂ at which Hb is 50% saturated is referred to as P₅₀. At a normal pH, Hb 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 tissues is a product of oxygen content and cardiac output. When Hb is near 100% saturated, blood contains approximately 20 mL of oxygen per 100 mL or 200 mL/L. In a healthy adult, 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.

Clinical observations and interpretation of blood gas values are critical in localizing the site of the lesion and estimating its severity (Table 421.3). 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

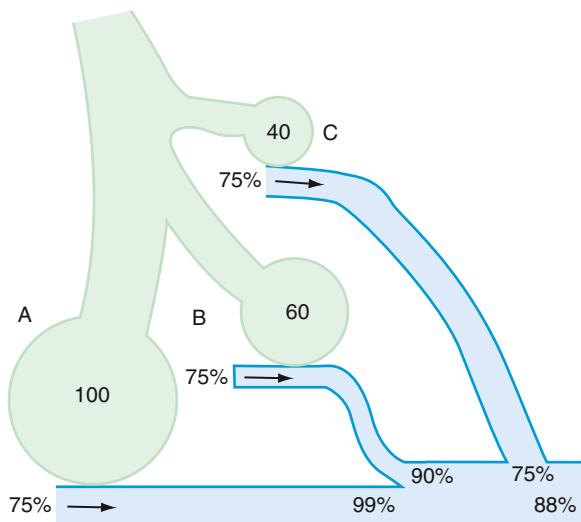


Fig. 421.4 Diagram demonstrating the effects of decreased ventilation-perfusion ratios on arterial oxygenation in the lungs. Three alveolar-capillary units are illustrated. Unit A has normal ventilation and an alveolar P_{O_2} of 100 mm Hg (shown by the number in the middle of the space). The blood that circulates through this unit raises its oxygen saturation from 75% (the saturation of mixed venous blood) to 99%. Unit B has a lower ventilation-perfusion ratio and a lower alveolar P_{O_2} of 60 mm Hg. The blood that circulates through this unit reaches a saturation of only 90%. Finally, unit C is not ventilated at all. Its alveolar P_{O_2} is equivalent to that of the venous blood, which travels through the unit unaltered. The oxygen saturation of the arterial blood reflects the weighted contributions of these three units. If it is assumed that each unit has the same blood flow, the arterial blood would have a saturation of only 88%. Ventilation-perfusion mismatch is the most common mechanism of arterial hypoxemia in lung disease. Supplemental oxygen increases the arterial P_{O_2} by raising the alveolar P_{O_2} in lung units that, like B, have a ventilation-perfusion ratio >0 .

Table 421.3 Interpretation of Arterial Blood Gas Values

Lesion	Effect	Typical ABG
Central (above the carina) airway obstruction or Depressed respiratory center or Ineffective neuromuscular function	Uniform alveolar hypoventilation	Early increase in P_{CO_2} . Proportionate decrease in P_{O_2} depending on alveolar air equation Response to supplemental oxygen: excellent
Intrapulmonary airway obstruction	Venous admixture mismatch	Mild: ↓ P_{CO_2} , ↓ P_{O_2} Moderate: "normal" P_{CO_2} , ↓ P_{O_2} Severe: ↑ P_{CO_2} , ↓ P_{O_2} Response to supplemental oxygen: good
Alveolar-interstitial pathology	Diffusion defect R → L shunt	Early decrease in P_{O_2} depending on severity Normal or low P_{CO_2} , ↑ P_{CO_2} if fatigue develops Response to supplemental oxygen: fair to poor

ABG, Arterial blood gas.
Courtesy Dr. Ashok Sarnaik.

has a higher P_{O_2} and lower P_{CO_2} , whereas that coming from hypoventilated regions has a lower P_{O_2} and higher P_{CO_2} . A lower blood P_{CO_2} can compensate for the higher P_{CO_2} because the Hb- CO_2 dissociation curve is relatively linear. In mild disease, the hyperventilated areas predominate, resulting in hypocarbia. An elevated P_{AO_2} in hyperventilated areas cannot compensate for the decreased P_{AO_2} in hypoventilated areas because of the shape of the O_2 -Hb dissociation curve. This results in venous admixture, arterial desaturation, and decreased P_{AO_2} (see Fig. 421.4). With increasing disease severity, more areas become hypoventilated, resulting in normalization of P_{CO_2} with a further decrease in P_{AO_2} . A normal or slightly elevated P_{CO_2} 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 hypercarbia, respiratory acidosis, and hypoxemia. The degree to which supplemental oxygenation raises P_{AO_2} 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. P_{CO_2} is either normal or decreased. An increase in P_{CO_2} is observed only later in the course, as muscle fatigue and exhaustion result in hypoventilation. Response to supplemental oxygen is relatively poor with shunting and diffusion disorders compared with other lesions.

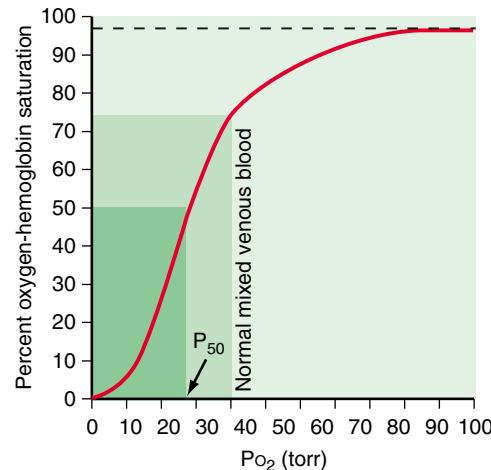


Fig. 421.5 Oxygen-hemoglobin dissociation curve. P_{50} of adult blood is around 27 torr. Under basal conditions, mixed venous blood has a P_{O_2} of 40 torr and oxygen-hemoglobin saturation of 75%. In arterial blood, these values are 100 torr and 97.5%, respectively. Note that there is a steep decline in oxygen-hemoglobin saturation at $P_{O_2} < 50$ torr, but relatively little increase in saturation is gained at $P_{O_2} > 70$ torr. (Courtesy Dr. Ashok Sarnaik.)

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.

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 Hb concentration, the clinical detection by inspection is an unreliable sign of hypoxemia. Arterial hypertension, tachycardia, and diaphoresis are late, and not exclusive, signs of hypoventilation.

Blood gas exchange is evaluated most accurately by the direct measurement of arterial pressure of oxygen (Po_2), pressure of carbon dioxide (PCO_2), 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 less invasive 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 $Po_2 < 85$ 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 $PCO_2 > 45$ mm Hg usually indicate hypoventilation or a severe ventilation-perfusion mismatch, unless they reflect respiratory compensation for metabolic alkalosis (see Chapter 73).

In general practice **pulse oximetry** is used to monitor a patient's peripheral arterial saturation (SpO_2). This noninvasive method uses spectrophotometry to assess oxygenated and deoxygenated hemoglobin ratios to determine the SpO_2 . Values are most accurate with arterial saturations above 90%; with saturations <90%, the accuracy is reduced. *Pulse oximetry often produces falsely high SpO_2 values in Black and dark-skinned patients, creating a risk for missed (occult) hypoxia, which may lead to underuse of oxygen therapy for Black patients.*

TRANSILLUMINATION OF THE CHEST

In infants up to at least 6 months of age, a pneumothorax (see Chapter 132) 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 helpful in interpreting findings. This test is unreliable in older patients and in those with subcutaneous emphysema or atelectasis.

RADIOGRAPHIC TECHNIQUES

Chest X-Rays

A posteroanterior and a lateral view (upright and in full inspiration) should be obtained, except in situations in which the child is medically unstable (Fig. 421.6). Portable images, although useful in the latter situation, can give a somewhat distorted image. Expiratory images can be misinterpreted, although a comparison of expiratory and inspiratory images may be useful in evaluating a child with a suspected foreign body (localized failure of the lung to empty reflects bronchial obstruction; see Chapter 435). Although images taken in a recumbent position are difficult to interpret when there is fluid within the pleural space or a cavity, if pleural fluid is suspected (see Chapter 451), decubitus images are indicated.

Upper Airway Film

A lateral view of the neck can yield invaluable information about upper airway obstruction (see Chapter 433) and particularly about the condition of the retropharyngeal, supraglottic, and subglottic spaces (which should also be viewed in an anteroposterior projection) (Fig. 421.7).

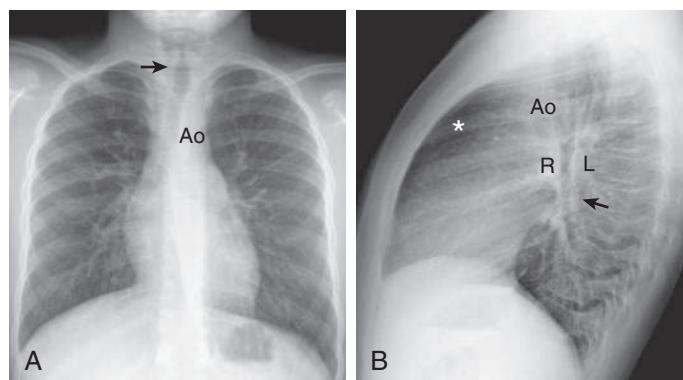


Fig. 421.6 Normal appearance of the trachea and lungs on chest radiography. A, On the frontal view, there is normal shoulder of the subglottic trachea (arrow). The trachea courses inferiorly with a fairly uniform diameter to the level of the carina apart from a mild, smooth indentation at the level of the aortic arch (Ao). The lungs are symmetrically inflated, with normal arborization of the vasculature. The hemidiaphragms are domed, not flattened. The normal heart size is less than 50% of the transverse dimension of the chest. B, On the lateral view, the trachea is of uniform diameter to the level of the aortic arch, with the exception of a mild, smooth impression from the aortic arch anteriorly (Ao). The hemidiaphragms are domed. The heart occupies less than 50% of the anteroposterior dimension of the chest and should not fill the retrosternal clear space (asterisk). The bronchus intermedius (arrow) courses posterior to the right pulmonary artery (R), and the arch of the left pulmonary artery (L) projects posterior to the carina. (From Walters MM, Robertson RL, eds. *Pediatric Radiology: The Requisites*, 4th ed. Philadelphia: Elsevier; 2017: Fig. 2.11.)

Knowing the phase of respiration during which the film was taken is often essential for accurate interpretation. Magnified airway images are often helpful in delineating the upper airways. Patients with suggested obstruction should not be unattended in the radiology department.

Sinus and Nasal Images

The general utility of radiologic examination of the sinuses is uncertain because a large number of images have positive findings (low sensitivity and specificity). Imaging studies are not necessary to confirm the diagnosis of sinusitis in children younger than age 6 years. CT scans are indicated if surgery is required, in cases of complications caused by sinus infection, in immunodeficient patients, in those with cystic fibrosis, and for recurrent infections unresponsive to medical management.

Chest Ultrasound

Chest ultrasound, which has no radiation and is more available in low-resource settings, has been shown to have more sensitivity and similar specificity in diagnosing community-acquired pneumonia compared to chest x-ray. Chest ultrasound can also detect pleural effusions and differentiate atelectasis from pneumonia.

Chest Computed Tomography

Chest CT often provides images of higher quality and sensitivity compared with radiography. Chest CT identifies early abnormalities such as air trapping, mucus plugging, or bronchiectasis in young children with cystic fibrosis before pathologic changes are detectable by either plain chest radiographs or pulmonary function testing. However, several caveats must be noted. Conventional chest CT involves higher radiation doses than plain images (see Chapter 758). The time required to perform chest CT examinations and the complications of respiratory and body motion mandate the use of sedation for this procedure in many infants and young children. However, improvements in imaging protocols and techniques have drastically reduced required radiation doses and imaging time. Chest CT is particularly useful in evaluating pulmonary nodules, pleural lesions, solid or cystic parenchymal lesions, pulmonary embolism, bronchiectasis, interstitial lung disease, and air trapping. The use of intravenous contrast material during CT

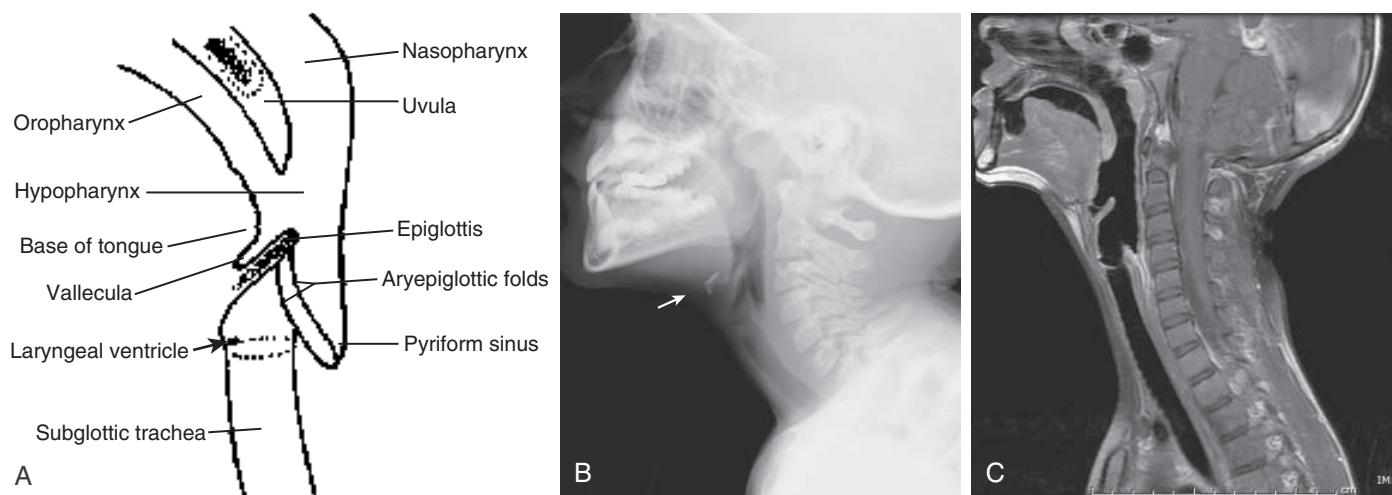


Fig. 421.7 A, Diagram depicting the normal anatomy of the upper airway. B, Corresponding lateral radiograph of the neck soft tissues. C, Sagittal T1-weighted magnetic resonance image. The hyoid bone “points to” the epiglottis on the radiograph (arrow). (From Walters MM, Robertson RL, eds. *Pediatric Radiology: The Requisites*, 4th ed. Philadelphia: Elsevier; 2017: Fig. 2.5.)

imaging enhances vascular structures, distinguishing vessels from other soft tissue densities.

Magnetic Resonance Imaging

Although CT is often considered the gold standard for chest imaging, advances in MRI techniques have broadened the indications for pediatric chest MRI. Pediatric chest MRI has shown utility in imaging several disease processes. In cases of pneumonia, chest MRI can be used to demonstrate pulmonary consolidation in addition to complications such as abscess, necrosis, and effusions with or without loculation. Congenital malformations can also be visualized using chest MRI. Bronchogenic cysts, congenital pulmonary airway malformation, sequestration, and pulmonary aplasia or agenesis can be well characterized using MR techniques. Furthermore, MRI can be applied to imaging congenital large airway disorders such as airway malacia and external airway compression caused by vascular rings and slings. Last, dynamic techniques using cine MR imaging provide four-dimensional imaging as airway structure changes throughout the breathing cycle. Cine MRI assesses both lower airway caliber in children with trachea or bronchomalacia and upper airway anatomy to diagnose a site of obstruction in children with obstructive sleep apnea. Aside from imaging time, MR may in some cases be inferior to CT for imaging of bronchiectasis without airway wall thickening, focal air trapping, signs of interstitial lung disease, and small pulmonary nodules. MR protocols currently vary across centers, and collaboration with radiologists experienced in specialized chest imaging will result in high-quality imaging with minimization of ionizing radiation while weighing the need for sedation.

Fluoroscopy

Fluoroscopy can be used to assess diaphragm function in cases of suspected paralysis and to differentiate from eventration. Occasionally, the modality is used to evaluate airway dynamics with the benefit of visualization during awake and spontaneous breathing. The use of ionizing radiation with this modality should be taken into consideration, especially if repeated studies in the same patient are undertaken. Procedures such as needle aspiration or biopsy of a peripheral lesion may be accomplished with the aid of fluoroscopy, CT, or ultrasonography.

Barium Swallow

A barium swallow study, performed with fluoroscopy and spot images, 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 and test for laryngeal penetration or pulmonary aspiration. Imaging of the esophageal phase is important and can be

used to detect the presence of esophageal dysfunction, vascular rings (see Chapter 434), and tracheoesophageal fistulas (see Chapter 365). 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 for this indication. Barium swallows have lower utility in evaluating gastroesophageal reflux (see Chapter 369).

Pulmonary Arteriography and Aortograms

Pulmonary arteriography has been used to allow detailed evaluation of the pulmonary vasculature. This imaging technique has also been helpful in assessing pulmonary blood flow and in diagnosing congenital anomalies, such as lobar agenesis, unilateral hyperlucent lung, vascular rings, and arteriovenous malformations. Thoracic aortograms demonstrate the aortic arch, its major vessels, and the systemic (bronchial) pulmonary circulation. They are useful in evaluating vascular rings and suspected sequestration.

Ventilation-Perfusion Relation and Radionuclide Lung Scans

Gravitational force pulls the lung away from the nondependent part of the parietal pleura. Consequently, alveoli and airways in the non-dependent parts (the upper lobes in upright position) of the lung are subjected to greater negative intrapleural pressure during tidal respiration and are kept relatively more inflated compared with the dependent alveoli and airways (the lower lobes in upright position). The nondependent alveoli are less compliant because they are already more inflated. Ventilation therefore occurs preferentially in the dependent portions of the lung that are more amenable to expansion during tidal inspiration. Although perfusion is also greater in the dependent portions of the lung because of greater pulmonary arterial hydrostatic pressure from gravity, the increase in perfusion is greater than the increase in ventilation in the dependent portions of the lung. Thus the ratios favor ventilation in the nondependent portions and perfusion in the dependent portions. Because the airways in the dependent portion of the lung are narrower, they close earlier during expiration. The lung volume at which the dependent airways start to close is referred to as the **closing capacity**. In normal children, the FRC is greater than the closing capacity. During tidal respiration, airways remain patent both in the dependent and the nondependent portions of the lung. In newborns, the closing capacity is greater than the FRC, resulting in perfusion of poorly ventilated alveoli during tidal respiration. Therefore normal neonates have a lower PaO_2 compared with older children.

The relationship is adversely affected in a variety of pathophysiologic states. Air movement in areas that are poorly perfused is referred to as **dead space ventilation**. Examples of dead space ventilation include

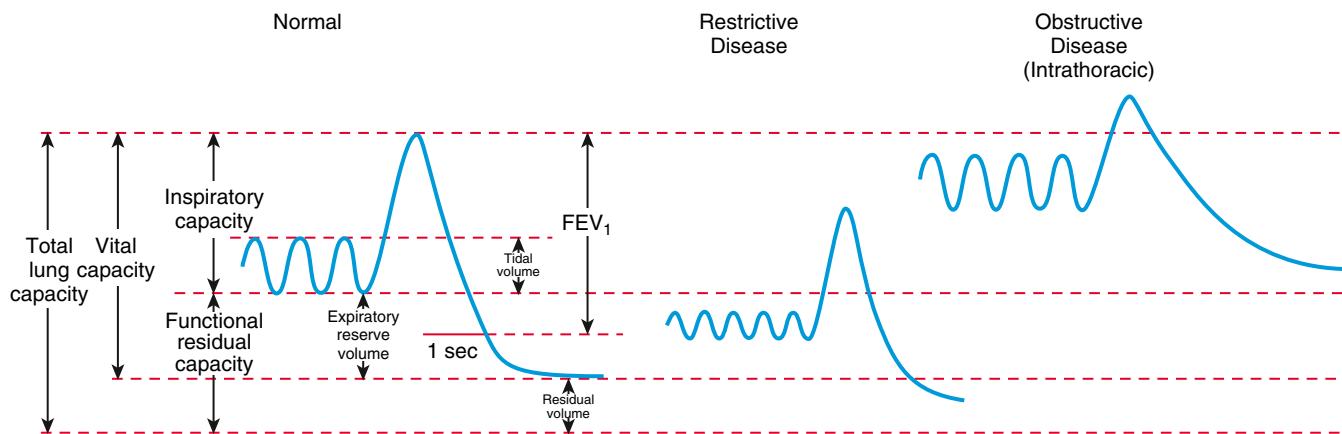


Fig. 421.8 Spirogram showing lung volumes and capacities. Forced expiratory volume 1 (FEV_1) is the maximum volume exhaled in 1 second after maximum inspiration. Restrictive diseases are usually associated with decreased lung volumes and capacities. Intrathoracic airway obstruction is associated with air trapping and abnormally high functional residual capacity and residual volume. FEV_1 and vital capacity are decreased in both restrictive and obstructive diseases. The ratio of FEV_1 to vital capacity is normal in restrictive disease but decreased in obstructive disease.

pulmonary thromboembolism and hypovolemia. Perfusion of poorly ventilated alveoli is referred to as **intrapulmonary right-to-left shunting** or **venous admixture**. Examples include pneumonia, asthma, and hyaline membrane disease. In intrapulmonary airway obstruction, the closing capacity is abnormally increased and can exceed the FRC. In such situations, perfusion of poorly ventilated alveoli during tidal respiration results in venous admixture.

The usual scan uses intravenous injection of material (macroaggregated human serum albumin labeled with ^{99m}Tc) 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, as well as 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 the demonstration of defects in the pulmonary arterial distribution that can occur with congenital malformations or pulmonary embolism. **Spiral reconstruction CT** with contrast medium enhancement is 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

Traditionally, lung volumes are measured with a spirogram (Fig. 421.8). **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** (VC) is defined as the amount of air moved in and out of the lungs through maximum inspiration and expiration. VC, inspiratory capacity, and expiratory reserve volume are decreased in lung pathology but are also effort dependent. **Total lung capacity** (TLC) is the volume of gas occupying the lungs after maximum inhalation.

The **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 inhalation, the patient forcefully exhales

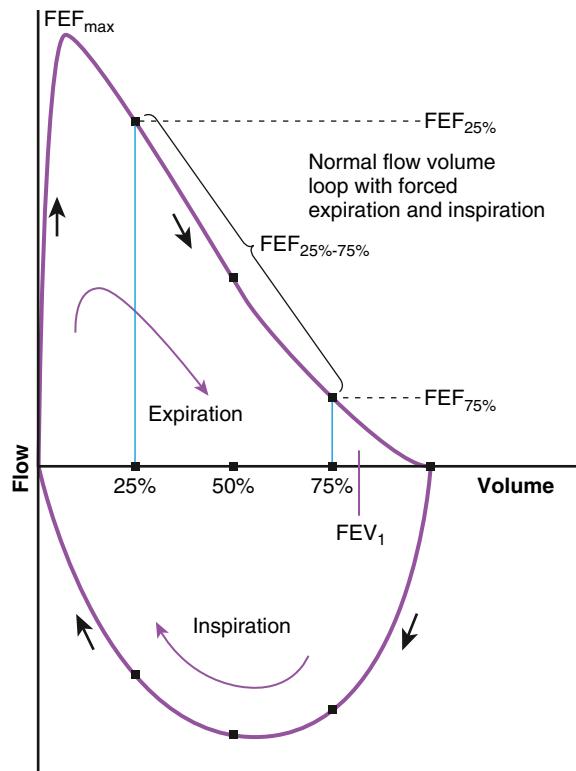


Fig. 421.9 Flow-volume loop in a normal person performed after maximal inspiration followed by forced complete expiration and forced complete inhalation. Maximum forced expiratory flow (FEF_{max}) represents maximum flow during expiration. This is attained soon after initiation of the expiration. Fall 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 (FEV₁), also termed **forced vital capacity** (FVC). FEV₁ is the amount of volume after 1 second of forced exhalation. Normally FEV₁ is around 80% of FVC. (Courtesy Dr. Ashok Sarnaik.)

through a mouthpiece into the device until residual volume is reached, followed by maximum inhalation (Fig. 421.9). Flow is plotted against volume. **Maximum forced expiratory flow** (FEF_{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

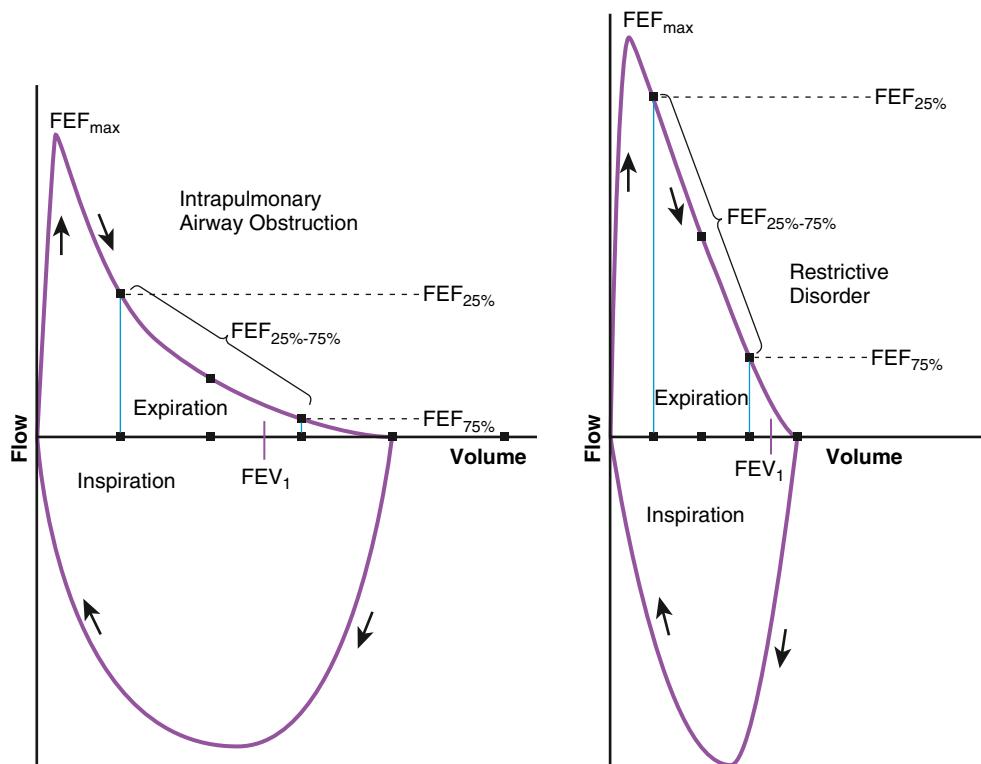


Fig. 421.10 Flow-volume loops in intrapulmonary airway obstruction and restrictive disorders. Note that in intrapulmonary airway obstruction, there is a decrease in maximum forced expiratory flow (FEF_{max}), $FEF_{25\%-75\%}$, and forced expiratory volume 1/forced vital capacity ($FEV_1/FVC\%$). The middle part of the expiratory loop appears concave. In restrictive disorders, the flow-volume loop assumes a more vertically oblong shape with reduction in FVC but not the $FEV_1/FVC\%$. Expiratory and inspiratory flow rates are relatively unaffected. (Courtesy Dr. Ashok Sarnaik.)

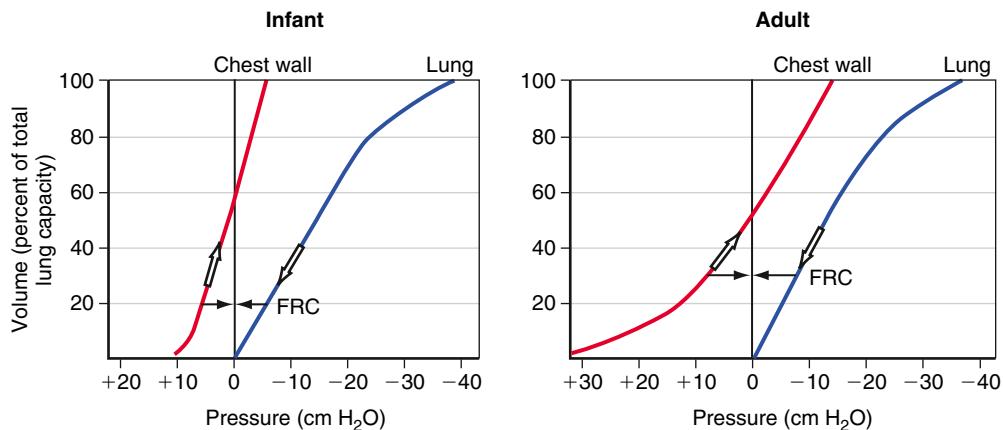


Fig. 421.11 Schematic of interaction between chest wall and lung recoil in infants compared with adults. The elastic recoil of a relatively more compliant chest wall is balanced by the lung recoil at a lower-volume functional residual capacity (FRC) in infants compared with adults. (Courtesy Dr. Ashok Sarnaik.)

(R_{AW}). The total volume exhaled during this maneuver is **forced vital capacity** (FVC). **Volume exhaled in 1 second** is referred to as **forced expiratory volume 1** (FEV₁). FEV₁/FVC is expressed as a percentage of FVC. FEF_{25-75%} is the mean flow between 25% and 75% of FVC, and is considered relatively effort independent. Individual values and shapes of flow-volume curves show characteristic changes in obstructive and restrictive respiratory disorders (Fig. 421.10). In intrapulmonary airway obstruction such as asthma or cystic fibrosis, there is a reduction of FEF_{max}, FEF_{25-75%}, FVC, and FEV₁/FVC. Also, there is a characteristic concavity in the middle part of the expiratory curve. In restrictive lung disease such as interstitial pneumonia (see Chapter 448.5) and kyphoscoliosis (see Chapter 467.5), FVC is decreased with relative preservation of airflow and FEV₁/FVC. The flow-volume curve assumes a vertically oblong shape compared with 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.

FRC has important pathophysiologic implications. 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's ribs because they 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 or the downward displacement of a domed diaphragm in an adult to expand the thoracic capacity. This creates an extremely high thoracic compliance compared with older children and adults (Fig. 421.11). The measured FRC in infants is higher than expected because infant respiratory muscles maintain the thoracic cage in an inspiratory position at all times. In addition, young infants experience some amount of air trapping during expiration.

Alveolar gas composition changes during inspiration and expiration. Alveolar PO_2 (PAO₂) increases and alveolar PCO_2 (PACO₂) decreases during inspiration as fresh atmospheric gas enters the lungs. During exhalation, PAO₂ decreases and PACO₂ increases as pulmonary capillary blood continues to remove oxygen from and add CO₂ into the alveoli (Fig. 421.12). FRC acts as a buffer, minimizing the changes in PAO₂ and PACO₂ during inspiration and expiration. FRC represents the

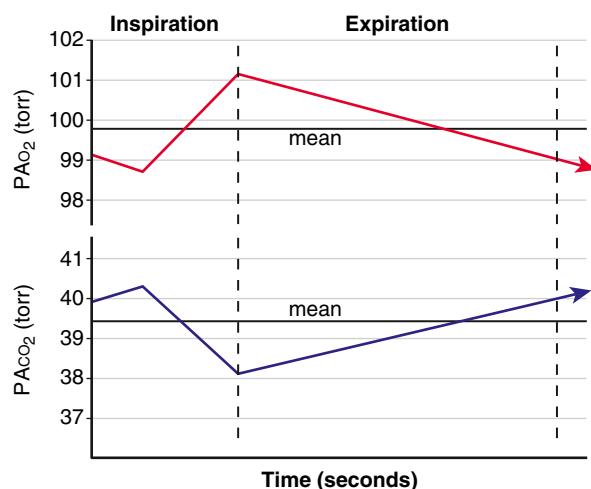


Fig. 421.12 Alveolar PO_2 rises and PCO_2 falls during inspiration as fresh atmospheric gas is brought into the lungs. During expiration, the opposite changes occur as pulmonary capillary blood continues to remove O_2 and add CO_2 from the alveoli without atmospheric enrichment. Note that during the early part of inspiration, alveolar PO_2 continues to fall and PCO_2 continues to rise because of inspiration of the dead space that is occupied by the previously exhaled gas. (Courtesy Dr. Ashok Sarnaik; modified from Comroe JH. *Physiology of Respiration*, 2nd ed. Chicago: Year Book Medical Publishers; 1974:12.)

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 PAO₂ during exhalation because a limited volume is available for gas exchange. PO₂ of pulmonary capillary blood therefore falls excessively during exhalation, leading to a decline in **arterial PO₂ (PAO₂)**. Any increase in PAO₂ (and therefore Pao₂) during inspiration cannot compensate for the decreased Pao₂ during exhalation. The explanation for this lies in the shape of the O₂-Hb dissociation curve, which is sigmoid shaped (see Fig. 421.5). Because most of the oxygen in blood is combined with Hb, it is the percentage of **oxyhemoglobin (SO₂)** that gets averaged rather than the PO₂. Although an increase in arterial PO₂ cannot increase O₂-Hb saturation >100%, there is a steep desaturation of Hb below a PO₂ of 50 torr; thus decreased SO₂ during exhalation as a result of low FRC leads to overall arterial desaturation and hypoxemia. The adverse pathophysiologic consequences of decreased FRC are ameliorated by applying **positive end-expiratory pressure (PEEP)** and increasing the inspiratory time during mechanical ventilation.

The lung pressure-volume relationship is markedly influenced by FRC (Fig. 421.13). Pulmonary compliance is decreased at abnormally low or high FRC.

FRC is abnormally increased in intrathoracic airway obstruction, which results in incomplete exhalation, and is abnormally decreased in alveolar-interstitial diseases. At excessively low or high FRC, tidal respiration requires higher inflation pressures compared to normal FRC. Abnormalities of FRC result in increased work of breathing with spontaneous respiration and increased barotrauma in mechanical ventilation.

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 TLC. TLC includes residual volume, which is

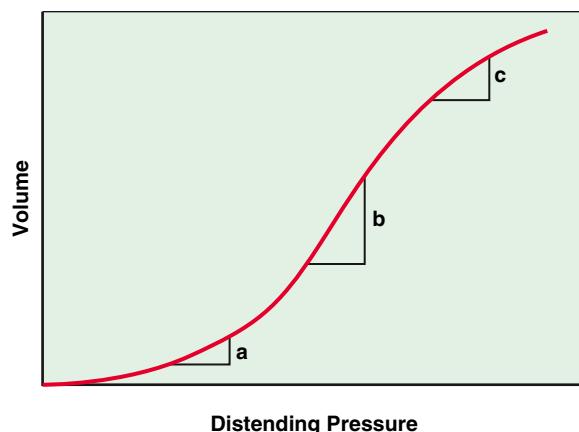


Fig. 421.13 Lung compliance is significantly influenced by the functional residual capacity (FRC). The same change in pressure is associated with less change in volume when FRC is abnormally decreased (a) or abnormally increased (c) compared with the normal state (b). (Courtesy Dr. Ashok Sarnaik.)

not accessible to direct determinations. It must therefore be measured indirectly by gas dilution methods or, preferably, by **plethysmography**. Restrictive disease also decreases VC. Obstructive diseases produce gas trapping and thus increase residual volume and FRC, particularly when these measurements are considered with respect to TLC.

Lung Clearance Index (LCI) is a test that uses multiple-breath washouts to demonstrate airway physiology. The test involves the gradual replacement of a tracer gas such as nitrogen, which is normally in the lungs or within biologically inert gas, with 100% oxygen. This gradual washout of the tracer gas requires no complex respiratory maneuvers but has some technical challenges. The variability of LCI in healthy children and adolescents is low, and LCI has been shown to discriminate against healthy individuals and patients with chronic conditions such as cystic fibrosis or asthma. LCI reports gas mixing efficiency, which is an index of lung function, with the diseased lung taking a longer time to wash out the tracer gas than a healthy lung. LCI has been shown to be able to detect lung disease before FEV₁ and therefore may be a tool for early detection of lung pathology.

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. 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. 421.8). A simple manometer can measure the maximal inspiratory and expiratory force a subject generates, normally at least 30 cm H₂O. This 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 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 (R_{AW}) is measured in a plethysmograph, or alternatively, the reciprocal of R_{AW} , **airway conductance**, may be used. Because R_{AW} measurements vary with the lung volume at which they are taken, it is convenient to use **specific airway resistance**, SR_{AW} ($SR_{AW} = R_{AW}/\text{lung volume}$), which is nearly constant in subjects older than age 6 years (normally <7 sec/cm H₂O).

Impulse oscillometry (IOS) is a tool that can be used in minimally cooperative patients such as young children. This technology uses properties of sound waves at different frequencies during normal tidal breathing to estimate resistance in airflow. This tool can differentiate small from large airway obstruction and measures bronchodilatory response. Although the tool is fairly easy to use, normative values are few, which limits the use across patients, but it may be a good tool to track airway resistance across time in conditions such as asthma.

The **diffusing capacity for carbon monoxide** is related to oxygen diffusion and is measured by rebreathing from a container with 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 confirming functional impairment in patients with 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. 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 R_{AW} 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 using a rapidly inflatable jacket. Gas dilution or plethysmographic methods can also be used in sedated infants to measure FRC and R_{AW} .

The measurement of **fractional exhaled nitric oxide** (FENO) is used as a surrogate measure for eosinophilic inflammation of the lower airways. It can be used as a part of a diagnostic evaluation for asthma, a tool for predicting or assessing an individual's response to antiinflammatory therapy, and in monitoring adherence to treatment. A number of commercially available devices are available for measurement of FENO. Some degree of cooperation is required, but FENO has been measured in preschool-age children. Normal cutoff values vary by age and device. FENO has been used to distinguish asthma (particularly allergic asthma) from other wheezing phenotypes. FENO achieves moderate diagnostic performance for the detection of asthma in children, with sensitivity, specificity, and diagnostic odds ratios of 0.79, 0.81, and 16.52, respectively. Children managed using FENO may have fewer asthma exacerbations. A decrease of FENO by 20% is considered

indicative of a positive response to antiinflammatory therapy. Some studies using FENO have contradictory results, and it is likely that FENO may be more useful in some asthma phenotypes than in others.

The measurement of **nasal nitric oxide** (nNO) is accomplished by collecting exhaled gas from a nostril during glottic closure and correlates to nasal mucosal inflammation. There is great interest in the use of nNO to diagnose **primary ciliary dyskinesia** (PCD, see Chapter 425), because of challenges diagnosing PCD with currently available techniques. A cutoff value of less than or equal to 77 nL/min showed excellent sensitivity and specificity using a standardized technique at multiple centers. Equipment for measurement of nNO is not yet FDA-approved in the United States.

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 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 alveolar 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. Specific bacteria in the lungs of children with cystic fibrosis (see Chapter 454) are linked to morbidity and mortality. There is a correlation between patient age and morbidity and mortality (as expected), but important microbes also are correlated either negatively or positively with early or late pathogenic processes. *Haemophilus influenzae* (see Chapter 240) is negatively correlated, and *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* (see Chapter 251.3) 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 who are younger patients with cystic fibrosis than the older and sicker population.

In addition, the microbiomes 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, but some bacteria,

such as *Haemophilus* and enterobacteria, are much more represented in the lungs than in the mouth. Principal differences in microbiome composition between smokers and nonsmokers are found in the mouth. For example, *Neisseria* levels are much lower in smokers as compared with nonsmokers. Overall, the microbiome diversity in smokers was also reduced compared with nonsmokers.

THE MICROBIOME

Whereas some studies have looked at the microbiome in the lungs and others in the gut, there is evidence to believe that there is a gut-lung axis regarding the microbiome. For example, the airway epithelium regulates local immunity (IgA antibodies, defensins) and can stimulate a Th2 airway response. Other cytokines are also involved such as transforming growth factor beta (TGFB). Bacteriophages are also important in the airways because these may protect the airways from certain bacteria. Importantly, the gut microbiome, influenced by many factors such as diet, environment, mode of childbirth, socioeconomic status, and antibiotic use, affects in a major way the development of immunity in the growing infant and child. Similarly, the lungs are not sterile, and bacteria exist in the lungs of children. It is possible therefore that the microbiome in one site affects the response to the microbiome in another through either immunity or predisposition to inflammation.

The Amish and Hutterite populations are genetically identical, but they have very different asthma prevalence, with the Hutterite having 4–6 times more asthma than the Amish population. One study showed that the Amish household had ~7 times more dust endotoxin. Extracts from the Amish dust inhibited airway hyper-responsiveness, but this did not happen from the Hutterite samples. Although this does not separate between the lung and gut, it suggests that the hygiene hypothesis is important and that microbes and immunity are tied together in the genesis of asthma, especially in children, and in the formative stages of immunity and allergic diseases.

Ciliary Structure and Function

Cilia are cellular organelles that project from respiratory epithelial surfaces into the lumen. They are microscopic hairlike structures, are motile, and beat in a coordinated fashion from distal to proximal airways to clear mucus, fluid, and inhaled particles. They generally beat at a fast pace, on the order of 10–20 Hz.

Their structure is typical, consisting of nine peripheral doublet microtubules arranged in a circular fashion, with two single microtubules centrally located. As such, this structure is called an *axoneme*. Each microtubule has an inner and an outer dynein arm, with radial spokes connecting each peripheral pair with the central microtubules.

Each epithelial cell lining the respiratory tract has around 200 such cilia. The cilia on the surface beat synchronously not only over the surface of one such cell but across many cells. How cells communicate to induce the rhythmic beating function of cilia across a sheet of cells is not well understood.

Hundreds of proteins make up each cilium in the respiratory tract, and many pathogenic variants have been described. Such variants render these cilia dysfunctional, leading to a respiratory disease, PCD. Often the structure is also abnormal, but cilia can be dysfunctional without an apparent EM abnormal structure (Fig. 421.14).

Cardiopulmonary Exercise Testing

Exercise testing (see Chapter 472.5) is a direct approach for measuring respiratory gas exchange and assessing causes of exercise limitations. 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 physiologic source of the symptom. Exercise is a strong provocateur of bronchospasm in susceptible patients, so exercise testing can be useful in the diagnosis of asthma as the cause of difficulty breathing with exertion. Several diseases or physiologic states distinct from asthma may mimic symptoms of exercise-induced bronchoconstriction. In addition to cardiac disease and decreased fitness, exercise-induced laryngeal obstruction (EILO) leads to significant limitations. In selected cases, performance of laryngoscopy during cardiopulmonary

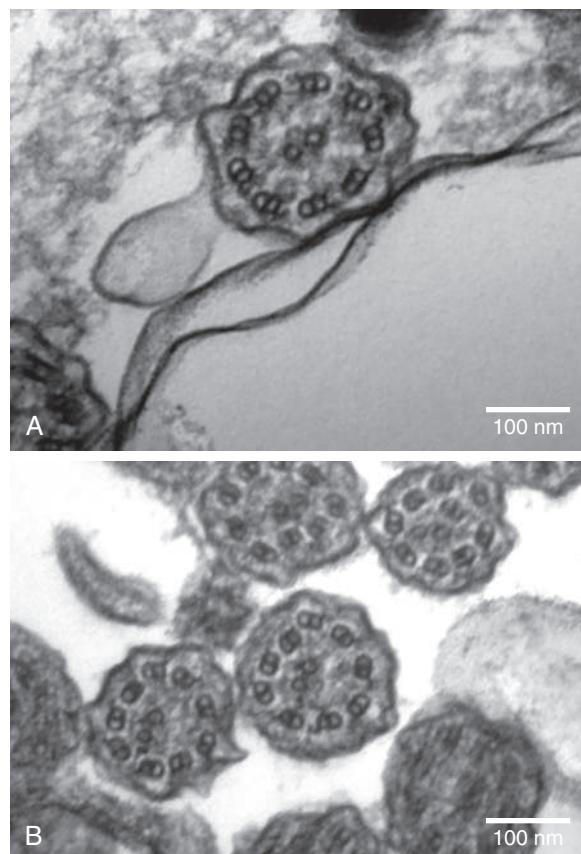


Fig. 421.14 A, Cross-section of a normal EM cilium structure. Note the typical axoneme structure, consisting of the nine peripheral doublet microtubules arranged in a circular fashion, with two single microtubules centrally located. Each microtubule has an inner and an outer dynein arm. B, Abnormal axoneme, as there are a number of doublets missing the dynein arms, which are clear in A, with normal cilium. Note also the disorganized location of the nine peripheral microtubules in some of the cilia. (Courtesy Dr. Denise Malicki, UCSD/Rady Children's Hospital.)

exercise testing lends essential diagnostic information. Application of cardiopulmonary testing for assessment of aerobic fitness and disease limitations provides invaluable diagnostic information to aid clinicians investigating exercise intolerance.

Sleep Studies

See Chapter 31.

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. Flexible bronchoscopy is commonly used in pediatrics to visualize the airways. There are several sizes of scopes that enable visualization of the proximal and distal airways. Many fiberoptic bronchoscopes also have a channel that allows for the collection of fluids, or in larger scopes allows for the insertion of tools such as forceps, baskets, or brushes. The smallest scope is a 2.2-mm-outer-diameter bronchoscope that does not have a channel; therefore only visualization of the airways is possible. The smallest bronchoscope with a channel is a 2.8-mm-outer-diameter scope, which has a 1.2-mm working channel. This scope is commonly used in pediatrics and is predominately used to visualize the airways and to collect a lavage sample. In larger “adult” scopes (4.9–5.5 mm outer diameter and 2.0 mm working channel), small instruments such as forceps can be inserted. Therapeutic bronchoscopes require an even larger channel (2.8 mm working channel, which requires a larger outer diameter of 6.0–6.3 mm), so they are not used often in the pediatric population. A smaller scope (4.1 mm outer diameter) with a larger working channel (2.0 mm) has become available and may make interventional pediatric bronchoscopy more common in the future. For urgent or emergent therapeutic interventions, such as foreign body aspiration or large volume hemoptysis, surgical rigid bronchoscopy remains the preferred approach, as it provides the largest working channel and permits simultaneous ventilation during the procedure.

Visualization of the airway has improved through advances in optics and insertable tools. **Narrow-band imaging** and **autofluorescence** imaging bronchoscopes are two types of bronchoscopes that can aid in the detection of airway lesions. These scopes appear no different than the conventional bronchoscope but use different bandwidths of lights to highlight mucosal and submucosal vasculature. These bronchoscopes allow the operator to see airway mucosal lesions that would be difficult to see or not be seen under normal white light. The auto-fluorescence imaging bronchoscope uses the fluorophores, such as tryptophan, collagen, elastin, and porphyrins, within the airway tissue to emit fluorescence when irradiated with a light source. Changes in concentrations of the fluorophores in bronchial mucosa would appear as an irregular lesion when viewed with an autofluorescence imaging bronchoscope. The narrow-band imaging bronchoscope also uses light absorption characteristics of Hb to enhance images of blood vessels. This bronchoscope uses blue wavelengths in the range of 390–445 nm to visualize the mucosal layer capillaries and green wavelengths at 530 and 550 nm to detect deeper submucosal thick blood vessels. Both types of bronchoscopes allow the operator to detect findings that would not be seen under normal white light. These scopes are being used more often in adults, where lesions are biopsied to detect premalignant and malignant lesions, although use has been described to better delineate characteristics of a subglottic cyst in a 3-month-old infant. These scopes are noninvasive and would be well tolerated in children, but are currently only available in larger “adult” sizes.

The most common diagnostic tool used in conjunction with fiberoptic bronchoscopy is **bronchoalveolar lavage (BAL)**. 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. It 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 in intubated patients by instilling and withdrawing saline through a catheter passed though the artificial airway and blindly wedged into a distal airway, although nonbronchoscopic BAL is less accurate and therefore has less reliable results. 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 and removing tissue masses. It is also indicated in patients with massive hemoptysis. In other cases, the flexible scope has multiple advantages: 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.

Transbronchial and endobronchial biopsies. Transbronchial biopsies are performed by passing forceps (1.2 mm pediatric or 2.0 mm adult) through the distal visualized airways to sample small airways and alveolar tissues. Transbronchial biopsy (TBB) in children is standard practice to monitor the lung allograft after transplantation, either as a surveillance or clinically indicated procedure. For the nontransplant patient, transbronchial biopsies can be used to facilitate the diagnosis of diffuse lung disease (such as interstitial pneumonitis, bronchiolitis obliterans, lymphoma, eosinophilic pneumonia, sarcoidosis, or hypersensitivity pneumonia) or large focal processes (such as infections or unresolving pneumonia). Transbronchial biopsies do produce smaller samples than video-assisted thoracoscopic surgery (VATS) or open lung biopsies, but with a lower attendant risk; the risk of pneumothorax has been estimated to be 2–8%. Endobronchial biopsies can be performed in children, but there are relatively few clinical situations where they are broadly applied.

The **endobronchial ultrasound (EBUS)**, is a scope that allows ultrasound images to be captured from the tip of the scope and also contains a working channel to collect a needle biopsy. This technology is particularly useful in the evaluation of mediastinal lymph nodes. This scope may be useful in the diagnosis of other conditions such as sarcoidosis, tuberculosis, and the staging of lung cancers. EBUS has been investigated in older pediatric patients as an alternative to CT-guided transthoracic fine needle aspiration for the evaluation of mediastinal lymph nodes and can be safely performed in children age 9+ years. A meta-analysis of 153 pediatric patients revealed a pooled sampling adequacy and combined diagnostic yield of EBUS of 98% (95% confidence interval [CI], 92–100%) and 61% (95% CI, 43–77%), respectively, and was generally safely tolerated.

Bronchial thermoplasty (BT) is a technology that can be used to treat patients with severe asthma. This technique uses the working channel of a fiberoptic bronchoscope to deliver targeted thermal energy to the airways to ablate the airway smooth muscle (ASM). The ablation of ASM may reduce the ability to bronchoconstrict. It may also affect the ASM's role in immunomodulation, ultimately altering the pathophysiology of asthma. BT requires a minimum of a 2.0-mm working channel, which limits this technology to bronchoscopes of at least an outer diameter of 4.1 mm. BT is performed over three bronchoscopy sessions to ablate different sections of the lung: right lower lobe, left lower lobe, and bilateral upper lobes. The right middle lobe is usually not ablated because of the potential risk of stenosis. The treatments are divided into three separate procedures to allow for shorter procedure times (30–60 minutes per session) and decrease the risk of widespread irritation. Patients are also given oral steroids for 3 days before the procedure to decrease airway inflammation associated with the ablation procedure. Although BT is gaining momentum in the treatment of severe asthma in the adult population, the long-term ramifications of ASM ablation in a child are still unknown. In adult studies that investigated BT as a therapeutic tool for asthma, small studies

demonstrated an improvement in clinical symptoms, and in a smaller cohort of patients (12 patients), no significant structural abnormalities were seen on chest radiographs 5 years after the procedure.

Complications: Regardless of the instrument used, the procedure performed, or the resulting 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, with increased complications when concomitant biopsies are taken. 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. Post-bronchoscopy 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, allowing the operator to view the surface of the lung, the pleural surface of the mediastinum and the 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. In general, 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, so they 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 less than $2,000/\text{mm}^3$ with a predominance of mononuclear cells, and low lactate 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 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 in expert hands there is low morbidity. Biopsy through the 3.5-mm-diameter pediatric bronchoscopes limits the sample size and diagnostic abilities. In addition to ensuring that an adequate specimen is obtained, the surgeon can inspect the lung surface and choose the site of biopsy. In older children, transbronchial biopsies can be performed using flexible forceps through a bronchoscope, an endotracheal tube, a rigid bronchoscope, or an endotracheal tube, usually with fluoroscopic

guidance. This technique is most appropriately used when the disease is diffuse, as in the case of *Pneumocystis* pneumonia, or after rejection of a transplanted lung. The diagnostic limitations related to the small size of the biopsy specimens can be mitigated by the ability to obtain several samples. The risk of pneumothorax related to bronchoscopy is increased when transbronchial biopsies are part of the procedure; however, the ability to obtain biopsy specimens in a procedure performed with topical anesthesia and conscious sedation is advantageous.

Genetic Testing

Genetic testing enables precise diagnosis of an expanding array of respiratory diseases. In addition to diagnosis, genetic testing can contribute to discussions of disease severity and prognosis, aids counseling surrounding family planning, and serves as a cornerstone for development and application of novel therapeutics. Applications range from identification of known diseases in a child with nonspecific symptoms to early identification in an otherwise asymptomatic individual. Whole genome sequencing can be applied to rapidly diagnose children presenting with rare diseases or new phenotypes of known disorders.

Acute respiratory distress in the neonatal period rarely occurs secondary to several known genetic disorders. Genetic testing can be considered for *full-term* infants with unexplained severe respiratory disease or premature infants with lung disease *out of proportion* to what would be expected for gestational age. Genetic pulmonary disorders causing neonatal respiratory distress include surfactant dysfunction from pathogenic variants in *ABCA3*, *SFTPB*, or *SFTPC* genes; brain-lung-thyroid syndrome due to variants in *NKX2-1*; pulmonary alveolar proteinosis associated with abnormalities in the granulocyte macrophage colony-stimulating factor (GM-CSF) receptor; and primary disorders of lung development, such as alveolar capillary dysplasia, caused by pathogenic variants in *FOXF1*.

Although disorders associated with obstructive lung disease, abnormal mucus clearance, and bronchiectasis may present at any age, newborn screening for cystic fibrosis can often facilitate genetic diagnosis in infancy with subsequent early interventions to prevent or slow the onset of lung disease. Although cystic fibrosis is a monogenic disorder, pathogenic variants in many different genes cause PCD. Presently, the spectrum of genetic variants leading to PCD has not yet been fully identified, and the disease should still be suspected even if a genetic panel is negative. As clinical genetic panels and understanding of variants of unknown significance expand, it is expected that diagnosis of PCD will streamline.

Several systemic diseases associated with diffuse lung disease can be diagnosed genetically, including Birt-Hogg-Dube, Ehlers-Danlos, Marfan, hereditary hemorrhagic telangiectasia, and Hermansky-Pudlak syndrome. Children presenting with unexplained alveolar hypoventilation suspected of congenital central hypoventilation syndrome should undergo *PHOX2B* pathogenic variant specific testing, the gold standard for diagnosis. The previous disorders are only a partial list of the many known childhood diseases associated with a genetic and respiratory component. When there is high suspicion for a genetic condition but gene panels or single-gene analysis are normal, practitioners can pursue whole exome/genome sequencing. Whole exome/genome sequencing can also be applied as first-line genetic testing in critically ill patients in need of rapid diagnosis. Genetic counseling is paramount when pursuing genetic testing, especially in the pediatric population. The spectrum of diseases able to be diagnosed using genetic testing will continue to grow and is expected to not only encompass the rare disorders discussed earlier but also the more common respiratory disorders seen in childhood.

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Chapter 422

Chronic or Recurrent Respiratory Symptoms

Anne G. Griffiths

Respiratory tract symptoms, including cough, dyspnea, wheeze, and stridor, may persist for long periods in a 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 likely underlying pathogenic mechanism; selecting the simplest effective therapy for the underlying process, which often is only symptomatic therapy; and then carefully evaluating its effect. 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 respiratory tract illness may be life-threatening or associated with the potential for chronic disability are listed in Table 422.1. If none of these findings is detected, the chronic respiratory process is less likely to be serious. 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., with 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 of recurrent or persistent cough 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 422.2 lists some of the conditions responsible for chronic cough. Table 422.3 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 a 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 or vaping history in older children and adolescents or the presence of a smoker in the home (Table 422.4).

The physical examination can provide further 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 often seen in most patients with bronchiectasis but in only a few other respiratory conditions with chronic cough (see Table 422.2). Tracheal deviation suggests foreign body aspiration, pleural effusion, a mediastinal mass or an enlarged lymph node.

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 years of age. Children who cough as often as several times a minute with regularity are likely to have a habit (tic) cough (see Chapter 37). If the cough is loose, every effort should be made to obtain sputum; many older children can comply. It is sometimes possible to pick up sputum with a throat swab quickly inserted into the lower pharynx while the child coughs with the tongue protruding. Clear mucoid sputum is most often associated with an allergic reaction or asthmatic bronchitis. Cloudy (purulent) sputum suggests a respiratory tract infection but can also reflect increased cellularity (eosinophilia) from an asthmatic process. Very purulent sputum is characteristic of bronchiectasis (see Chapter 452). Malodorous expectorations suggest anaerobic infection of the lungs. In cystic fibrosis (see Chapter 454), the sputum, even when purulent, is rarely foul smelling.

Laboratory tests can help in the evaluation of a chronic cough. Sputum quality assessment includes a low number of squamous epithelial cells, found only in the upper airway, and a higher number of leukocytes. However, laboratories use different values, and in the case of cystic fibrosis, pathogens found are associated with lower respiratory infection even in the absence of satisfactory quality by various criteria. Sputum eosinophilia suggests asthma, asthmatic bronchitis, or hypersensitivity reactions of the lung (see Chapter 448), but a polymorphonuclear cell response suggests infection; if sputum is unavailable, the presence of eosinophilia in nasal secretions also suggests atopic disease. If most of the cells in sputum are macrophages, postinfectious hypersensitivity of cough receptors should be suspected. Sputum macrophages can be stained for hemosiderin content, which is diagnostic of pulmonary hemosiderosis (see Chapter 457), or for lipid content, which in large amounts suggests, but is not specific for, repeated aspiration. Rarely, children may expectorate partial casts of the airway, which can be characterized by investigating causes of plastic bronchitis. However, in young children, bronchoalveolar lavage may be needed for optimal ascertainment of alveolar macrophages. Children whose coughs persists for more than 6 weeks should be tested for cystic fibrosis regardless of their race or ethnicity (see Chapter 454). 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 457) or hemoptysis, or eosinophilia that accompanies asthma and other hypersensitivity reactions of the lung. Infiltrates on the chest radiograph suggest cystic fibrosis, bronchiectasis, foreign body, hypersensitivity pneumonitis, tuberculosis, or other infection. 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,

Table 422.1 Indicators of Serious Chronic Lower Respiratory Tract Disease in Children

Persistent fever
Ongoing limitation of activity
Failure to grow
Failure to gain weight appropriately
Clubbing of the digits
Persistent tachypnea and labored ventilation
Shortness of breath and exercise intolerance
Chronic purulent sputum
Persistent hyperinflation
Substantial and sustained hypoxemia
Refractory infiltrates on chest x-ray
Persistent pulmonary function abnormalities
Hemoptysis
Family history of heritable lung disease
Cyanosis and hypercarbia
Unusual (opportunistic) or recurrent nonpulmonary infections

Table 422.2 Differential Diagnosis of Recurrent and Persistent Cough in Children

RECURRENT COUGH	
Asthma	
Drainage from upper airways	
Aspiration	
Frequently recurring respiratory tract infections in immunocompetent or immunodeficient patients	
Symptomatic Chiari malformation	
Idiopathic pulmonary hemosiderosis	
Hypersensitivity (allergic) pneumonitis	
PERSISTENT COUGH	
Hypersensitivity of cough receptors after infection	
Reactive airway disease (asthma)	
Chronic sinusitis	
Chronic rhinitis (allergic or nonallergic)	
Bronchitis or tracheitis caused by infection or smoke exposure	
Bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, immunodeficiency	
Tic cough	
Foreign body aspiration	
Recurrent aspiration owing to pharyngeal incompetence, tracheolaryngoesophageal cleft, or tracheoesophageal fistula	
Gastroesophageal reflux, with or without aspiration	
Pertussis	
Extrinsic compression of the tracheobronchial tract (vascular ring, neoplasm, lymph node, lung cyst)	
Tracheomalacia, bronchomalacia	
Endobronchial or endotracheal tumors	
Endobronchial tuberculosis	
Hypersensitivity pneumonitis	
Fungal infections	
Inhaled irritants, including tobacco smoke	
Irritation of external auditory canal	
Angiotensin-converting enzyme inhibitors	

tests for gastroesophageal reflux (see Chapter 369), and special microbiologic studies including rapid viral testing. Evaluation of ciliary morphology, nasal endoscopy, laryngoscopy, and bronchoscopy may also be indicated.

Tic cough or somatic cough disorder (psychogenic cough or habit cough) 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

Table 422.3 Characteristics of Cough and Other Clinical Features and Possible Causes

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

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

Modified from Chang AB, Landau LI, Van Asperen PP, et al. Cough in children: definitions and clinical evaluation. Thoracic Society of Australia and New Zealand. Med J Aust. 2006;184(8):398–403, Table 2.

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 highly successful. Self-hypnosis is another successful therapy, often effective with one session. The designation "tic cough" or "somatic cough disorder" is preferable to "habit cough" or "psychogenic cough" because it carries no stigma and because most of

Table 422.4 Clinical Clues About Cough

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

From Kliegman RM, Greenbaum LA, Lyle PS. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: WB Saunders; 2004:19.

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 croupy cough and hoarse voice. Stridor is most commonly observed in children with croup (see Chapter 433); foreign bodies and trauma can also cause acute stridor. A

Table 422.5 Causes of Recurrent or Persistent Stridor in Children

RECURRENT
Allergic (spasmodic) croup
Respiratory infections in a child with otherwise asymptomatic anatomic narrowing of the large airways
Laryngomalacia
PERSISTENT
Laryngeal obstruction
Laryngomalacia
Papillomas, hemangiomas, other tumors
Cysts and laryngocoles
Laryngeal webs
Bilateral abductor paralysis of the cords
Foreign body
Tracheobronchial disease
Tracheomalacia
Subglottic tracheal webs
Endobronchial, endotracheal tumors
Subglottic tracheal stenosis, congenital or acquired
Extrinsic masses
Mediastinal masses
Vascular ring
Lobar emphysema
Bronchogenic cysts
Thyroid enlargement
Esophageal foreign body
Tracheoesophageal fistula
OTHER
Gastroesophageal reflux
Macroglossia, Pierre Robin syndrome
Cri-du-chat syndrome
Paradoxical vocal cord dysfunction
Hypocalcemia
Vocal cord paralysis
Chiari crisis
Severe neonatal episodic laryngospasm caused by SCN4A pathogenic variant

few children, however, acquire recurrent stridor or have persistent stridor from the first days or weeks of life (Table 422.5). Most congenital anomalies of large airways that produce stridor become symptomatic soon after birth. Increase of stridor when a child is supine suggests **airway malacia**, such as 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 (with wheezing) that accompanies physical activity and is not responsive to asthma therapies, **paradoxical vocal cord dysfunction** may be considered. 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 resulting from changes of body position should be assessed. Anteroposterior and lateral radiographs, contrast esophagography, fluoroscopy, computed tomography (CT), and magnetic resonance imaging (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 439.

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 intra-thoracic 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 421). Children younger than 2-3 years 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 weeks suggests other diagnoses. Most recurrent or persistent wheezing in children is the result of airway reactivity. Nonspecific 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 434). Wheezing that attends cystic fibrosis is most common in the first year 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 448.5). 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 second 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 should be considered if the response is unsatisfactory.

RECURRENT AND PERSISTENT LUNG INFILTRATES

Radiographic lung infiltrates resulting from acute pneumonia usually resolve within 1-3 weeks, but a substantial number of children, particularly infants, fail to completely clear infiltrates within a 4-week period. These children may be febrile or afebrile and may display a wide range of respiratory symptoms and signs. Persistent or recurring infiltrates present a diagnostic challenge (Table 422.6).

Table 422.6

Diseases Associated with Recurrent, Persistent, or Migrating Lung Infiltrates Beyond the Neonatal Period

Aspiration	Pharyngeal incompetence (e.g., cleft palate)
	Laryngotracheoesophageal cleft
	Tracheoesophageal fistula
	Gastroesophageal reflux
	Lipid aspiration
	Neurologic dysphagia
	Developmental dysphagia
Congenital anomalies	
	Lung cysts (congenital pulmonary airway malformation)
	Bronchopulmonary sequestration
	Congenital lobar emphysema
	Bronchogenic cysts
	Bronchial stenosis or aberrant bronchus
	Vascular ring
	Congenital heart disease with large left-to-right shunt
	Pulmonary lymphangiectasia
Genetic conditions	
	Cystic fibrosis
	Primary ciliary dyskinesia
	Sickle cell disease (acute chest syndrome)
Immunodeficiency, phagocytic deficiency	
	Humoral, cellular, combined immunodeficiency states
	Chronic granulomatous disease and related phagocytic defects
	Hyper-immunoglobulin E syndromes
	Complement deficiency states
Immunologic and autoimmune diseases	
	Asthma
	Allergic bronchopulmonary aspergillosis
	Hypersensitivity pneumonitis
	Pulmonary hemosiderosis
	Collagen-vascular diseases
	Granulomatosis with polyangiitis
Infection, congenital	
	Cytomegalovirus
	Rubella
	Syphilis
Infection, acquired	
	Cytomegalovirus
	Tuberculosis
	HIV
	Other viruses
	Chlamydia
	Mycoplasma, Ureaplasma
	Pertussis
	Fungal organisms
	Pneumocystis jiroveci
	Visceral larva migrans
	Inadequately treated bacterial infection
Interstitial pneumonitis and fibrosis	
	Usual interstitial pneumonitis
	Lymphocytic interstitial pneumonia (AIDS)
	Nonspecific interstitial pneumonia (NSIP)
	Genetic disorders of surfactant synthesis, secretion
	Desquamative interstitial pneumonia
	Cryptogenic organizing pneumonia
	Acute interstitial pneumonia (Hamman-Rich syndrome)
	Alveolar proteinosis
	Drug-induced, radiation-induced inflammation and fibrosis
Neoplasms and neoplastic-like conditions	
	Primary or metastatic pulmonary tumors
	Leukemia
	Histiocytosis
	Eosinophilic pneumonias
Other etiologies	
	Bronchiectasis (congenital, postinfectious)
	Sarcoidosis

Symptoms associated with chronic lung infiltrates in the first 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 such as in **middle lobe syndrome** (see Chapter 444), wheezing, and cough may reflect asthma, even in the first year 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 first year 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 164, 167, and 172). Primary ciliary dyskinesia is also of consideration in patients with frequent otitis media and suppurative sinopulmonary disease, with or without accompanying heterotaxy or history of neonatal respiratory distress (see Chapter 455). 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 444). Traction bronchiectasis may also be suggested on radiography with persistent findings in a given region of the film after a 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 or immunocompromise (see Chapter 322). A history of paroxysmal coughing in an infant suggests pertussis syndrome or cystic fibrosis. Persistent infiltrates in a toddler, especially with loss of volume, may 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 456), *Pneumocystis jiroveci* infection (see Chapter 290), 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, primary ciliary dyskinesia, 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 422.6. Cytologic evaluation of sputum, if available, may be helpful. Chest CT often provides more precise anatomic detail concerning the infiltrate or further characterizes 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 Chapters 434-438). 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. Ciliary biopsy may be obtained from the inferior epithelial surface of nasal turbinates or from the lower airway during bronchoscopy. 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 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 airway clearance 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.

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422.1 Extrapulmonary Diseases with Pulmonary Manifestations

John Palla and Susanna A. McColley

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, and 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 somatic 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 (no history of asthma) children but more often has a neuromuscular, musculoskeletal, or inflammatory etiology. **Cyanosis** can be caused by cardiac and/or hematologic disorders. **Dyspnea** and **exercise intolerance** can have a number of extrapulmonary causes. These extrapulmonary 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 422.7 lists more common extrapulmonary causes of such symptoms.

EVALUATION

In the evaluation of a child or adolescent with respiratory symptoms, it is important to obtain a detailed medical history, family history, and review of systems to evaluate the possibility of extrapulmonary origin. A comprehensive physical examination is also essential to identify signs of 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. Pulmonary 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 422.8 lists disorders that commonly have respiratory complications.

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Table 422.7 Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Chest pain	Musculoskeletal	Inflammation (overuse, postviral, idiopathic), injury	Reproducible pain with palpation
Chest pain	Cardiac disease	Inflammation (pericarditis), ischemia (anomalous coronary artery, vascular disease)	Precordial pain, friction rub on examination; exertional pain, radiation to arm or neck
Chest pain	Gastroesophageal reflux disease	Esophageal inflammation and/or spasm	Heartburn, abdominal pain
Cyanosis	Congenital heart disease	Right-to-left shunt	Neonatal onset, lack of response to oxygen
	Methemoglobinemia	Increased levels of methemoglobin interfere with delivery of oxygen to tissues	Drug or toxin exposure, lack of response to oxygen
Dyspnea	Toxin exposure, drug side effect, or overdose	Variable, but often metabolic acidosis	Drug or toxin exposure confirmed by history or toxicology screen, normal oxygen saturation measured by pulse oximetry
	Anxiety, panic disorder	Increased respiratory drive and increased perception of respiratory efforts	Occurs during stressful situation, other symptoms of anxiety and/or depression
Exercise intolerance	Anemia	Inadequate oxygen delivery to tissues	Pallor, tachycardia, history of bleeding, prolonged or heavy menstrual periods, history of inadequate diet
Exercise intolerance	Deconditioning	Self-explanatory	History of inactivity, obesity
Hemoptysis	Nasal bleeding	Posterior flow of bleeding leads to suspicion of pulmonary origin	History and physical findings suggest nasal source; normal chest examination and chest radiography
	Upper gastrointestinal tract bleeding	Hematemesis mimics hemoptysis	History and physical examination suggest gastrointestinal source; normal chest examination and chest radiography
Wheezing, cough, dyspnea	Congenital or acquired cardiac disease	Pulmonary overcirculation (atrioseptal defect, ventriculoseptal defect, patent ductus arteriosus), left ventricular dysfunction	Murmur Refractory to bronchodilators Radiographic changes (prominent pulmonary vasculature, pulmonary edema)
Wheezing, cough	Gastroesophageal reflux disease	Laryngeal and bronchial response to stomach contents	Emesis, pain, heartburn
		Vagally mediated bronchoconstriction	Refractory to bronchodilators

Table 422.8 Disorders with Frequent Respiratory Tract Complications

UNDERLYING DISORDER(S)	RESPIRATORY COMPLICATIONS	DIAGNOSTIC TESTS
Autoimmune disorders	Pulmonary vascular disease, restrictive lung disease, pleural effusion (especially systemic lupus erythematosus), upper and lower airway disease (granulomatosis with polyangiitis)	Spirometry, lung volume determination, oximetry, diffusing capacity of the lung for carbon monoxide, chest radiography, upper airway endoscopy, and/or CT
Central nervous system disease (static or progressive)	Aspiration of oral or gastric contents, impaired airway clearance	Chest radiography, videofluoroscopic swallowing study, esophageal pH probe, fiberoptic bronchoscopy
Immunodeficiency	Infection, bronchiectasis, impaired mucociliary clearance	Chest radiography, fiberoptic bronchoscopy, chest CT
Liver disease	Pleural effusion, hepatopulmonary syndrome	Chest radiography, assessment of platypnea-orthodeoxia
Malignancy and its therapies	Infiltration, metastasis, malignant or infectious effusion, parenchymal infection, graft versus host disease (bone marrow transplant), fibrosis	Chest radiography, chest CT, fiberoptic bronchoscopy, lung biopsy
Neuromuscular disease	Hypoventilation, atelectasis, pneumonia, restrictive lung disease, impaired airway clearance	Spirometry, lung volume determination, respiratory muscle force measurements
Obesity	Restrictive lung disease, obstructive sleep apnea syndrome, asthma	Spirometry, lung volume determination, nocturnal polysomnography

Chapter 423

Sudden Infant Death Syndrome

Fern R. Hauck, Rebecca F. Carlin,
Rachel Y. Moon, and Carl E. Hunt

Sudden infant death syndrome (SIDS) is defined as the sudden, unexpected death of an infant that remains unexplained after a thorough postmortem examination, which includes a complete autopsy, investigation of the scene of death, review of the medical history, and appropriate laboratory testing. An autopsy is essential to identify possible natural explanations for sudden unexpected death such as congenital anomalies or infection and to diagnose nonaccidental trauma. 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 generally encompasses all SUIDs that occur during sleep, including SIDS (ICD-10 R95), accidental suffocation and strangulation in bed (ICD-10 W75), and ill-defined deaths, also known as *undetermined* (ICD-10 R99).

EPIDEMIOLOGY

SIDS, accidental suffocation and strangulation in bed, and ill-defined deaths are among the most common causes of overall infant mortality. SIDS is one of the leading causes of postneonatal (28 days to 1 year of age) mortality. 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 per year) before 1992, when it was recommended that infants sleep nonprone as a way to reduce the risk for SIDS. Since then, particularly after initiation of the national Back to Sleep (now called *Safe 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). There has been a slower rate of decline since that time; in 2020 the rate was 0.38 per 1,000 live births (~1,200 infants). The initial decline in the number of SIDS deaths in the United States and other countries has been largely 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. Although several other countries have decreased prone sleeping prevalence to ≤2%, in the United States in 2016, only 78% of infants were usually being placed supine for sleep. Among Black infants, these rates were even lower, at 62%.

There is increasing evidence that infant deaths previously classified as SIDS are now being classified by medical examiners and coroners as the result of other causes, notably **accidental suffocation and strangulation in bed** (ICD 10 W75) and **ill-defined deaths** (ICD 10 R99). Between 1994 and 2018, there was a sevenfold increase in the rate of accidental suffocation and strangulation in bed, from 0.03 to 0.22 deaths per 1,000 live births. There was also a 57% increase in the rate of ill-defined deaths between 1995 and 2018, from 0.21 to 0.33 deaths per 1,000 live births. These sudden and unexpected infant deaths are primarily associated with unsafe sleeping environments, including side and prone positioning, sharing a sleep surface with others, and soft bedding in the sleep environment. 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 that will be described later are applicable to all sleep-related SUID.

PATHOLOGY

There are no autopsy findings *pathognomonic* for SIDS, and no findings are required for the diagnosis, but some findings are commonly seen on postmortem examination (Table 423.1). Petechial hemorrhages are found in 68–95% of infants who died of SIDS 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 (see Table 423.1). Nearly 65% of these infants have structural evidence of preexisting, chronic, low-grade asphyxia, and other studies have identified biochemical markers of asphyxia. Infants who died of SIDS have higher levels of vascular endothelial growth factor (VEGF) in the cerebrospinal fluid (CSF). These increases may be related to VEGF polymorphisms (see “Genetic Risk Factors” and Table 423.3) or might indicate recent hypoxic events because VEGF is upregulated by hypoxia.

Numerous studies have shown brain abnormalities that may cause or contribute to an impaired autonomic response to an exogenous stressor, including in the hippocampus and brainstem, the latter being the major area responsible for respiratory and autonomic regulation (see Table 423.1). The primary affected sites of chemoreception and respiratory drive include peripheral chemoreceptors (e.g., carotid body) and multiple central chemoreceptors, including the retrotrapezoid nucleus, serotonergic raphe nuclei, locus coeruleus, orexinergic neurons, solitary tract nucleus, and the dorsal motor nucleus of the vagus.

The ventral medulla has been a particular focus for studies in infants who died of SIDS (see Table 423.1). It is an integrative area for vital autonomic functions, including breathing, arousal, and chemosensory function. 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 sudden intrauterine unexplained deaths also have hypoplasia of the arcuate nucleus. Imaging mass spectroscopy of postmortem medullary tissue has identified abnormal expression of multiple peptides, especially in the raphe, hypoglossal, and pyramidal nuclei that include components for developmental neuronal/glial/axonal growth, cell metabolism, cytoarchitecture, and apoptosis. These findings suggest that SIDS infants have abnormal neurologic development

Table 423.1 Common Postmortem and Research Pathologic Abnormalities Observed in Sudden Infant Death Syndrome Infants

COMMON OBSERVATIONS

Petechial hemorrhages, lungs, and pleura
Pulmonary edema

RESEARCH FINDINGS

Evidence of preexisting chronic low-grade asphyxia
Increased cerebrospinal levels of vascular endothelial growth factor (VEGF)

- Secondary to preexisting asphyxia
- VEGF polymorphisms

NEUROPATHOLOGY RESEARCH FINDINGS

Abnormalities leading to impaired autonomic responses
Peripheral and central chemoreceptor abnormalities
Ventral medullary abnormalities

- Hypoplastic arcuate nucleus
- Abnormalities in serotonin (5-HT) neurons
- Decreases in 5-HT_{1A} and 5-HT_{2A} receptor immunoreactivity
- Extensive serotonergic brainstem abnormalities

contributing to pathogenesis, with the impairments suggesting delayed neurologic maturation.

Neurotransmitter studies of the arcuate nucleus have also identified several receptor abnormalities 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 (see Table 423.1). High neuronal levels of interleukin (IL)-1 β are present in the arcuate and dorsal vagal nuclei in infants with SIDS compared with 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, arousal, cardiovascular control, circadian regulation and non-rapid eye movement (NREM) sleep, thermoregulation, and upper airway reflexes. Decreases in 5-HT_{1A} and 5-HT_{2A} receptor immunoreactivity have been observed in the dorsal nucleus of the vagus, solitary nucleus, and ventrolateral medulla. There are extensive serotoninergic brainstem abnormalities in infants with SIDS, including increased 5-HT neuronal count, a lower density of 5-HT_{1A} 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 (see Table 423.1). Male infants with SIDS have lower receptor-binding density than do female infants with SIDS. Overall, these 5-HT-related studies suggest that the synthesis and availability of 5-HT are decreased within 5-HT pathways, and medullary tissue levels of 5-HT and its primary biosynthetic enzyme (tryptophan hydroxylase) are lower in infants with SIDS compared with age-matched controls. Although a subset of infants with SIDS has serotonergic abnormalities in serotonin neurons in the medullary reticular formation, the neuropathologic abnormalities in SIDS involve more than just a serotonergic deficiency in specific medullary nuclei and appear to involve failure of the network of neurochemical transmitters in various subcortical locations. For example, there is a complex relationship between serotonergic neurotransmission in the medulla and acetylcholine and nicotinic receptors.

ENVIRONMENTAL RISK FACTORS

Major risk factors for SIDS and SUID are outlined in Table 423.2 and include both nonmodifiable and modifiable risk factors.

The persistent ethnic disparities seen in SIDS and SUID rates likely reflect broader societal inequities. Low socioeconomic status (SES), unemployment, housing instability, and other factors that create barriers to optimal health outcomes are highly correlated with race/ethnicity in the United States and are also associated with both higher risk of SIDS and increased prevalence of known risk factors for these deaths (see the next section). Although these factors are consistently associated with higher risk, SIDS affects infants from all social strata. In the United States, Black, American Indian, and Alaska 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. Greater efforts are needed to address this persistent disparity and to ensure that SIDS risk-reduction education reaches all parents and other care providers, including other family members and personnel at daycare centers.

Table 423.2 Risk Factors Associated with Sudden Infant Death Syndrome

MATERNAL AND ANTENATAL RISK FACTORS

- Elevated second-trimester serum α -fetoprotein
- Smoking
- Alcohol use
- Drug use (cocaine, heroin)
- Nutritional deficiency
- Inadequate prenatal care
- Low socioeconomic status
- Younger age
- Lower education
- Single marital status
- Shorter interpregnancy interval
- Intrauterine hypoxia
- Fetal growth restriction

INFANT RISK FACTORS

- Age (peak 1–4 mo)
- Male gender
- Ethnicity (Black, American Indian, Alaska Native)
- Growth failure
- No breastfeeding
- No pacifier (dummy)
- Preterm birth
- Prone and side sleep position
- Recent febrile illness (mild infections)
- Inadequate immunizations
- Smoking exposure (prenatal and postnatal)
- Unsafe sleep environment, including soft sleeping surface, soft bedding
- Bed sharing with parent(s) or other children
- Sleeping in a room separate from parent(s)
- Thermal stress, overheating
- Colder season, no central heating

Nonmodifiable Environmental Risk Factors

Infants are at greatest risk of SIDS at 1–4 months of age, with most deaths having occurred by 6 months. 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 by SIDS than are female infants.

Modifiable Environmental Risk Factors

Pregnancy-Related Factors

An increased SIDS risk is associated with numerous obstetric factors, suggesting that the *in utero* environment of future SIDS infants is suboptimal. SIDS infants are more commonly of higher birth order, independent of maternal age, and of gestations after shorter interpregnancy intervals. Parents of SIDS infants generally receive less prenatal care and initiate care later in pregnancy, and this likely reflects difficulties in accessing care. In addition, low birthweight, preterm birth, and slower intrauterine and postnatal growth rates are risk factors.

Cigarette Smoking

There is a major association between **intrauterine exposure to cigarette smoking** and risk for SIDS. The incidence of SIDS was 2–3 times greater among infants of mothers who smoked in

studies conducted before SIDS risk-reduction campaigns and 4 times higher in studies after implementation of SIDS risk-reduction campaigns. The risk of death is progressively greater as daily cigarette use increases. The effects of smoking by the infant's father and other household members are more difficult to interpret because they are highly correlated with maternal smoking. There appears to be a small independent effect of paternal smoking, but data on other household members have been inconsistent. The effect of prenatal smoking on SIDS risk is not believed to be caused by lower birthweight, which is often found among infants of smoking mothers, but more likely because of alterations in autonomic function, cardiovascular reflexes, or arousal making the infants more vulnerable to a sleep-related death.

It is difficult to assess the independent effect of infant exposure to **environmental tobacco smoke** because parental smoking behaviors during and after pregnancy are also highly correlated. However, a twofold increased risk of SIDS is found for infants exposed only to postnatal maternal environmental tobacco smoke. There is a dose-response for the number of household smokers, number of people smoking in the same room as the infant, and the number of cigarettes smoked. These data suggest that keeping the infant free of environmental tobacco smoke can further reduce an infant's risk of SIDS.

Drug and Alcohol Use

Most studies link maternal **prenatal drug use**, especially opiates, with an increased risk of SIDS, ranging from a 2- to 15-fold increased risk. Studies looking at the association between maternal **alcohol use** prenatally or postnatally and SIDS have conflicting results. In one study, periconceptional alcohol use and binge drinking in the first trimester were associated with a sixfold and an eightfold increased risk of SIDS, respectively. Similarly, a study from Western Australia found that a report of maternal alcohol use during pregnancy was associated with an almost sevenfold increased risk of SIDS. 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 hours before the infant died carried an eightfold increased risk of SIDS. Siblings of infants with fetal alcohol syndrome have a 10-fold increased risk of SIDS compared with controls. Although there are conflicting reports of illicit drug use and SIDS overall, prenatal drug use, especially opiates, is associated with an increased risk of SIDS, ranging from 2- to 15-fold. Data on cannabis use and SIDS are extremely limited, with only one study from New Zealand reporting results for postpartum maternal use. This study found that nighttime cannabis use was associated with a twofold increased risk of SIDS, whereas daytime use was not associated with increased risk.

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 are 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: 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 may be related to the relative instability of the position. Infants who are placed on their side and roll to prone are at exceptional risk, with one study finding they are almost 9 times

more likely to die of SIDS than those placed supine. Although the majority of SIDS occurrences are still associated with infants being found prone, a higher proportion of SIDS is now attributed to being placed on the side for sleeping than for being placed 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, such as those with anatomic or functional upper airway compromise when supine.

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. However, 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. 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 and Soft or Loose Bedding. Infants should sleep on firm, flat, noninclined surfaces without soft or loose bedding. Soft sleep surfaces and soft or loose bedding, including comforters, pillows of any kind, bumper pads, stuffed animals, mattress toppers, pillow-top mattresses, sheepskins, polystyrene bean pillows, and old or soft mattresses, are associated with increased risk of SIDS. Infant sleep positioners, including pillows and wedges, which are often marketed to hold infants on their side or at an angle to help with reflux, are also not recommended. Based on available research, swaddling infants, or wrapping them in a blanket, is not recommended as a strategy to reduce SIDS. Infants who roll to the prone position while swaddled are at particularly high risk of SIDS. Wearable blankets are an acceptable alternative. Weighted blankets, weighted sleepers, weighted swaddles, or other weighted objects should not be placed on or near the sleeping infant.

Overheating. Overheating, based on indicators such as higher room temperature, a history of fever, sweating, and excessive clothing or bedding, has been associated with increased risk of SIDS. 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.

Bed Sharing. 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, sofa, or other soft or confining sleeping surface; when the mother is a smoker; and when the bed sharer has used alcohol or arousal-altering drugs or medications. Infants younger than 4 months of age are at increased risk even when mothers are nonsmokers. A meta-analysis of 19 studies found that low-risk infants (i.e., those who were breastfed and never exposed to cigarette smoke in utero or after birth) still had a fivefold increased risk of SIDS until the age of 3 months 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. It is recommended that infants who are brought into the parents' bed for feeding or comforting be returned to their crib or bassinet when the parent is ready to sleep. Room sharing *without* bed sharing is associated with lower SIDS rates and is therefore recommended.

Commercial Devices Marketed to Reduce the Risk of SIDS. A large number of commercial devices have been marketed that claim to reduce the risk of SIDS or other sleep-related infant deaths, including in-bed sleepers, but there is no evidence that any of these devices reduce the risk of these deaths. A 2021 Consumer Product Safety Commission

ruling states that any infant sleep product must meet existing federal safety standards for cribs, bassinets, play yards, and bedside sleepers.

Infant Feeding Care Practices and Exposures

Breastfeeding Is Associated with a Lower Risk of Sudden Infant Death Syndrome.

A meta-analysis found that breastfeeding was associated with a 45% reduction in SIDS after adjusting for confounding variables and that this protective effect increased for exclusive breastfeeding compared with partial breastfeeding. A subsequent meta-analysis found that breastfeeding for under 2 months was not associated with a reduced risk of SIDS, but any breastfeeding for 2 months or more and exclusive breastfeeding for 2–6 months was associated with an approximate halving of risk. Nursing pillows are a risk factor for infant suffocation and should be avoided.

Pacifier use is associated with a lower risk of SIDS in the majority of studies. Although it is not known if this is a direct effect of the pacifier itself or from associated infant or parental behaviors, use of the pacifier is protective even if it is dislodged 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. However, well-designed clinical trials 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 who die of SIDS, 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 diphtheria, tetanus, and pertussis was half that for nonimmunized infants.

GENETIC RISK FACTORS

There are some genetic differences identified in infants who died of SIDS compared with healthy infants and to infants dying from other causes (see Table 423.3). Pathogenic gene variants occurring at higher incidence in SIDS infants compared with controls include multiple cardiac ion channelopathy genes that are proarrhythmic, autonomic nervous system development genes, proinflammatory genes related to infection and immunity, and several serotonin (5-HT) genes. In ~15% of patients with SIDS, postmortem gene sequencing reveals a specific monogenic pathogenic variant (see Table 423.4; Fig. 423.1). Some of these genes are more plausible than others in predisposing *infants* to sudden unexpected death.

Multiple studies have established the importance of a pathway to SIDS that involves cardiac sodium or potassium channel dysfunction resulting in either **long QT syndrome** (LQTS) or other pro-arrhythmic conditions (see Table 423.4 and Fig. 423.1). LQTS is a known cause of sudden death in children and adults as the result of a prolonged cardiac action potential causing either increased depolarization or decreased repolarization current. The first evidence supporting a causal role for LQTS in SIDS was a large Italian study in which a corrected QT interval >440 msec on an electrocardiogram (ECG) performed on days 3–4 of life was associated with an odds ratio of 41 for SIDS. Several case reports have subsequently provided proof of the concept that cardiac channelopathy polymorphisms are associated with SIDS. LQTS is associated with polymorphisms related mainly to gain-of-function variants primarily in the sodium channel gene (*SCN5A*) that encodes critical channel pore-forming α subunits or essential channel-interacting proteins. LQTS also is associated with mainly loss-of-function variants in potassium channel genes. **Short QT syndrome** (SQTS) is another cause of life-threatening arrhythmia or sudden death, often during

Table 423.3

Genetic Risk Factors for Sudden Infant Death Syndrome (SIDS): Observed Polymorphisms

- Multiple cardiac ion channelopathy genes
- Autonomic developmental genes
- Proinflammatory genes affecting infection and immunity
 - Increased proinflammatory function
 - Decreased antiinflammatory function
- Genes affecting both serotonergic and adrenergic neurons

Table 423.4

Identified and Possible Monogenic Associations with SIDS

ARRHYTHMIAS/CHANNELopathies

- LQTS* (*SCN5A*, *ANK2*, *CALM2*)
- SQTS (*KCNH2*, *KCNQ1*)
- Brugada syndrome* (*SCN5A*, *TRPM4*, *SCN3B*, *GPD1L*, *SCN10A*)
- Catecholaminergic polymorphic ventricular tachycardia* (*RYR2*)

EPILEPSY SYNDROMES

- Genes associated with sudden unexpected death in epilepsy (*SCN1A*, *DEPDC5*)
- Nondystrophic myotonia (*SCN4A*)
- Dravet syndrome (*SCN1A*)

METABOLIC DISORDERS

- Pyruvate dehydrogenase deficiency
- Medium-chain acyl-dehydrogenase deficiency
- Systemic primary carnitine deficiency
- Carnitine palmitoyltransferase deficiency
- Glutaric aciduria type II
- Maple syrup urine disease
- Congenital disorders of glycosylation
- Glycogen storage disease

CARDIAC/CARDIOMYOPATHIES*

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy (*RYR2*)
- Catecholaminergic ventricular tachycardia (*RYR2*, *CASQ2*, *CALM2*)
- Left ventricular noncompaction
- Marfan syndrome
- Mitral valve prolapse
- Ehlers-Danlos syndrome

*For many phenotypic disorders, most, but not all, genes have been identified
LQTS, Long QT syndrome; SQTS, short QT syndrome.

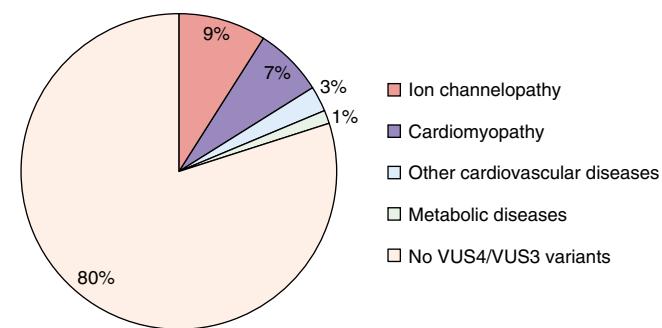


Fig. 423.1 Percentage of SIDS infants with likely causative variants in genes associated with cardiomyopathies, ion channelopathies, other cardiovascular diseases, and metabolic diseases. VUS, variant of unknown significance. (From Neubauer J, Lecca MR, Russo G, et al. Postmortem whole-exome analysis in a large sudden infant death syndrome cohort with a focus on cardiovascular and metabolic genetic diseases. *Eur J Hum Genetics*. 2017;25:404–409, Fig. 1.)

rest or sleep. Gain-of-function variants in genes including *KCNH2* and *KCNQ1* have been causally linked to SQTS, and some of these deaths have occurred in infants, suggesting that SQTS may also be causally linked to SIDS (see Table 423.4).

Other cardiac ion-related channelopathy pathogenic gene variants that are also proarrhythmic include Brugada syndrome (*BrS1*, *BrS2*) and catecholaminergic polymorphic ventricular tachycardia (*CPVT1*) (see Table 423.4). Collectively, these pathogenic variants in cardiac ion channels provide a lethal proarrhythmic substrate in some infants and may account for 5–10% or more of SIDS cases. In one study, using targeted massively parallel sequencing, 15.7–18.6% of Dutch SIDS cases were considered to be explained genetically by cardiac arrhythmias.

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 (MAOA) metabolizes both of these neurotransmitters, and a recent study has observed a high association between SIDS and low-expressing MAOA 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 in the promoter region of the 5-HTT protein gene occur with greater frequency in SIDS than in control infants. The long "L" allele increases effectiveness of the promoter and reduces extracellular 5-HT concentrations at nerve endings compared with the short "S" allele. The L/L genotype has been associated with increased 5-HT transporters in some studies of neuroimaging and postmortem binding, but more recent studies have not found any relationship between SIDS and the long (L) allele or the LL genotype.

An association has also been observed between SIDS and a 5-HTT intron 2 polymorphism, which differentially regulates 5-HTT expression. There were positive associations between SIDS and the intron 2 genotype distributions in Black infants who died of SIDS compared with Black 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 pathogenic variant has been identified in intron 2 of the *FEV* gene, and the distribution of this variant differs significantly in SIDS compared with control infants.

Molecular genetic studies in infants who died of SIDS have also identified pathogenic genetic variants pertinent to early embryologic development of the autonomic nervous system. Protein-changing pathogenic variants related to the *PHOX2a*, *RET*, *ECE1*, *TLX3*, and *EN1* genes have been identified, particularly in Black infants who died of SIDS. Eight polymorphisms in the *PHOX2B* gene occurred significantly more frequently in SIDS compared with control infants. Abnormalities in both the structure and expression of the *PHOX2B* gene, which is involved in neuronal maturation, have also been reported in significantly more SIDS infants than in controls. One study has reported an association between SIDS and a distinct tyrosine hydroxylase gene (*THO1*) allele, which regulates gene expression and catecholamine production.

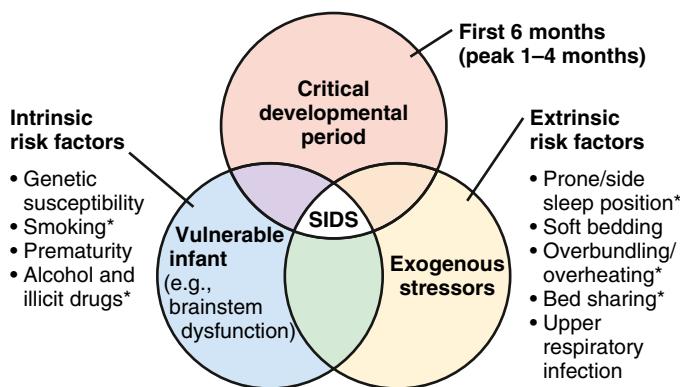
Multiple studies have observed altered expression of genes involved in the inflammatory process and immune system regulation. Differences in SIDS infants compared with controls have been reported for two complement *C4* genes. Some SIDS infants have loss-of-function polymorphisms in the gene promoter region for IL-10, another antiinflammatory cytokine. IL-10 polymorphisms associated with decreased IL-10 levels could contribute to SIDS by delaying initiation of protective antibody production or reducing capacity to inhibit inflammatory cytokine production. However, other studies have not found differences in IL-10 genes in SIDS infants compared with age-matched controls.

An association has been reported between single-nucleotide polymorphisms in the proinflammatory gene encoding IL-8 and SIDS infants found prone compared with SIDS infants found in other sleep positions. IL-1 is another proinflammatory gene, and a higher prevalence of the IL-1 receptor antagonist, which would predispose to higher risk for infection, has been reported in infants who died of SIDS. Significant associations with SIDS are also reported for polymorphisms in VEGF, IL-6, and tumor necrosis factor- α (TNF- α). These three 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 adverse imbalance between proinflammatory and antiinflammatory cytokines. As

apparent proof of principle, elevated levels of IL-6 and VEGF have been reported from CSF in SIDS infants. There were no group differences in the IL6-174G/C polymorphism in a Norwegian SIDS study, but the aggregate evidence nevertheless suggested an activated immune system in SIDS and implicated genes involved in the immune system. Almost all SIDS infants in one study had positive histories for prone sleeping and fever before death and positive HLA-DR expression in laryngeal mucosa, and high HLA-DR expression was associated with high levels of IL-6 in CSF.

GENE-ENVIRONMENT INTERACTIONS

Interactions between genetic and environmental risk factors determine the actual risk for SIDS in individual infants (see Fig. 423.2; Table 423.5). Equally important, there is a dynamic interaction between genetic or intrinsic vulnerability and the *sleep environment* (see Fig. 423.3). 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. However, infants with insufficient arousal responsiveness to hypoxia 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 genetic risk factors, such as ventilatory and arousal abnormalities and temperature or metabolic regulation deficits. Cardiorespiratory control deficits could be related to



*Modifiable risk factors

Fig. 423.2 Schematic of the triple-risk model for sudden infant death syndrome (SIDS) showing the critical interactions between intrinsic risk factors (including genetic risk factors) resulting in a vulnerable infant, a critical developmental period or age, and exogenous stressors or extrinsic risk factors. (Modified from Filiano JJ, Kinney HC. A perspective on the neuropathologic findings in victims of the sudden infant death syndrome: the triple risk model. *Biol Neonate*. 1994;65:194–197.)

Table 423.5 Interactions Between Genetic and Environmental Risk Factors that Determine the Actual Risk for SIDS in Individual Infants

GENETIC RISK FACTOR	ENVIRONMENTAL RISK FACTOR
Intrinsic vulnerability Impaired ventilatory and arousal responses	Sleep environment Nonsupine sleep position Soft bedding
Cardiac ion channelopathy	Sleep-related hypoxemia or hypercarbia leading to acidosis
Diminished immune responses to infections	Respiratory or other benign infections
Diminished brainstem autonomic control	Cigarette smoke exposure

5-HTT 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 sleep environment. 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 423.2). Benign infections might increase the risk for SIDS if interacting with genetically determined proinflammatory or impaired immune responses. 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 activation and degranulation, suggesting that increased susceptibility to an anaphylactic reaction is another genetic factor influencing fatal outcomes to otherwise minor infections. Interactions between upper respiratory infections or other minor illnesses and factors such as prone sleeping might also play a role in the pathogenesis of SIDS.

The increased risk of 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. Infant studies document decreased ventilatory and arousal responsiveness to hypoxia after fetal nicotine exposure, and impaired autoresuscitation 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. Tobacco smoke 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-monooxygenase 3 (*FMQ3*) is one of the enzymes that metabolizes nicotine, and a polymorphism has been identified that occurs more frequently in SIDS infants compared with controls and more frequently in infants whose mothers reported heavy smoking. This polymorphism would result in increased nicotine levels and hence is 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 significantly 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 if resulting in acidosis. The prone sleeping position is associated with increased sympathetic activity.

INFANT GROUPS AT INCREASED RISK FOR SUDDEN INFANT DEATH SYNDROME

Subsequent Siblings of an Infant Who Died of Sudden Infant Death Syndrome

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 versus 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 Table 423.5 and Figs. 423.2 and 423.3). Recurrent SIDS in a family should also alert the clinician to consider other causes of sudden and unexpected death, such as metabolic diseases, cardiac channelopathies, or nonaccidental causes.

Preterm Birth

Despite reductions of more than 50% in SIDS and SUID among infants born preterm since initiation of the Back to Sleep (Safe to Sleep) campaign in the United States in 1994, the risk of death remains significantly higher for these infants than for those born full term. The risk increases as gestational age decreases. Compared with infants born at 37–42 weeks, the odds ratio for SIDS is greatest for infants born at 24–28 weeks of gestation (2.57, 95% confidence interval 2.08, 3.17). Even at 33–36 weeks gestational age at birth, the risk of SIDS remains significantly increased compared with infants born at term. The peak chronological age for SIDS is later in infants born preterm, with chronological age at death inversely proportional to gestational age at birth.

Although infants born preterm are at increased risk for apnea, apnea of prematurity per se does not seem to be related to the increased SIDS risk. Premature infants' increased risk is instead likely related in part to immaturity of brainstem responses; physiologic studies have found impaired cortical arousals, lower baroreflex sensitivity, and impaired autonomic control. Sociodemographic and environmental risk are also important. Infants born preterm have more sociodemographic risk factors overall than infants born at term. In addition, infants born preterm are more likely to be placed prone at home; this may be in part because these infants are often placed prone while mechanically ventilated in the neonatal intensive care unit (NICU), and safe sleep practices are often not well-modeled during the remainder of the NICU admission. The association between prone position and SIDS in preterm and low birthweight infants is equal to or greater than this association in infants born full 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 who were believed to be at increased risk for SIDS, especially those with brief resolved unexplained events (BRUEs; see Chapter 424) and subsequent siblings of infants who died of SIDS. In the aggregate, these studies have indicated brainstem abnormalities in the neuroregulation of cardiorespiratory control or other autonomic functions and are consistent with the autopsy findings and genetic studies in infants who died of SIDS. In addition to physiologic abnormalities in chemoreceptor sensitivity, other observed physiologic abnormalities have been found in respiratory pattern, control of heart and respiratory rate or variability, and arousal responsiveness to asphyxial situations. A deficit in arousal responsiveness may be a necessary prerequisite for death to occur but may be insufficient to cause death in the absence of other genetic or environmental risk factors.

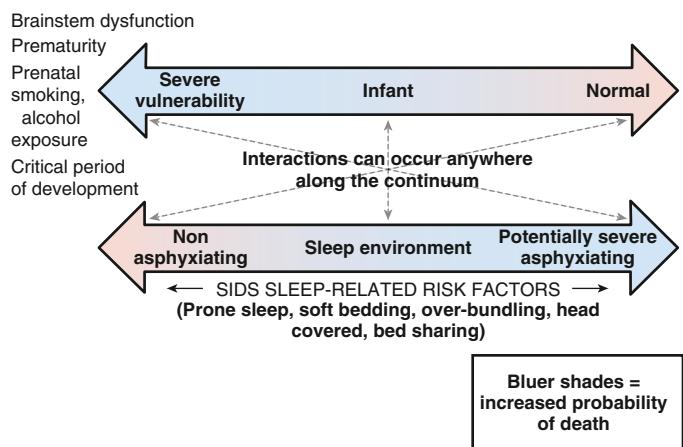


Fig. 423.3 Dynamic interactions between intrinsic vulnerability to sudden infant death syndrome (SIDS) and degree of risk in the sleep environment, ranging from nonasphyxiating (completely safe) to potentially severe asphyxiating (highly unsafe). Intrinsic vulnerability could be related to genetic risk factors, fetal or early infant exposures, or other factors. (Modified from Hunt CE, Darnall RA, McEntire BL, Hyma BA. Assigning cause for sudden unexpected infant death. *Forensic Sci Med Pathol*. 2015;11:283–288.)

Autoresuscitation (gasping) is a critical component of the arousal response to asphyxia, and a failure of autoresuscitation in infants may be the final and most devastating physiologic failure. In one study, most normal full-term infants younger than 9 postnatal weeks of age aroused in response to mild hypoxia, whereas only 10–15% of infants older than 9 weeks of age aroused. These data 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 infants who died of SIDS, suggesting that such infants may be predisposed to ventricular arrhythmia. Although this is consistent with the observations of cardiac ion channel gene polymorphisms in some infants who subsequently die of SIDS, there are no antemortem QT interval data for these infants that confirm the importance of this finding. Infants who were studied physiologically and then died of SIDS a few weeks later had higher heart rates and lower heart rate variability in all sleep-wake states and diminished heart rate variability during wakefulness. These infants also had longer QT intervals than control infants during both REM and NREM sleep, especially in the late hours of the night when SIDS most likely occurs. However, the QT interval exceeded 440 msec in only one of these infants who subsequently died.

It has been postulated that the decreased heart rate variability and increased heart rate observed in infants who later died of SIDS may in part be related to decreased vagal tone, perhaps from vagal neuropathy or brainstem damage in areas responsible for parasympathetic cardiac control. The power spectrum analysis of heart rate variability is one way to assess sympathetic and 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 infants may thus have different autonomic responsiveness to obstructive apnea, perhaps indicating impaired autonomic nervous system control associated with higher vulnerability to external or endogenous stresses, and hence reduced electrical stability of the heart; this may create a vulnerability for SIDS.

Home cardiorespiratory monitors with memory capability have recorded the terminal events in some infants who died of SIDS. However, these recordings did not include pulse oximetry and could not identify obstructed breaths because of reliance on transthoracic impedance for breath detection. In most instances, there was 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 prospectively infants who will go on to have SIDS, and no effective intervention has been established even if infants at risk 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. Although there are a growing number of consumer products marketed to monitor infants during sleep, there is no evidence that home electronic surveillance using existing technology reduces 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. Parental electrocardiographic screening is not helpful, in part because spontaneous pathogenic variants are common.

Reducing the Risk of SIDS and SUID

Reducing risk behaviors and increasing protective behaviors among infant caregivers to achieve further reductions and eventual elimination of SIDS and SUID is a critical goal. Plateaus in placing infants supine for sleep and persistent high rates of soft bedding use and surface sharing in the United States are cause for concern and require renewed educational efforts. Recent studies indicate soft or loose bedding is present in the sleep environment of greater than 50% of infants in the United States. A 2015 Centers for Disease Control and Prevention (CDC) survey of parents in 14 states and New York City found that 52.7% of White non-Hispanic, 76.5% of Black non-Hispanic, 66.7% of Hispanic, 76.8% of Asian or Pacific Islander, and 83.9% of American Indian or Alaska Native parents reported surface sharing with their infants. The American Academy of Pediatrics (AAP) guidelines for reducing infant deaths in the sleep environment were updated in 2022 and are aimed at 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 AAP 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.
- Infants should be put to sleep on a noninclined, 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 such sitting devices can increase the risk of gastroesophageal reflux and upper airway obstruction from head or neck flexion. Sleeping on an inclined surface can also increase the risk of head or neck flexion and makes it easier for infants to roll into an unsafe side or prone position.
- Feeding of human milk is recommended. Unless it is contraindicated or the parent is unable to do so, it is recommended that infants be fed with human milk (i.e., not offered any formula or other nonhuman milk-based supplements) exclusively for ~6 months, with continuation of human milk feeding for 1 year or longer as mutually desired by parent and infant.
- It is recommended that infants sleep in the same room as their parents but in their own crib or bassinet that conforms to the safety standards of the Consumer Product Safety Commission. Placing the crib or bassinet near the parents' bed facilitates feeding and contact. If parents bring the infant into the adult bed for feeding or comforting, the infant should be returned to a separate sleep surface when the parents are ready for sleep. Couches and armchairs are associated with an extremely high increased risk of SIDS, accidental suffocation, and entrapment and should never be used for infant sleep.
- There should be no soft materials and loose bedding in the infant's sleep environment (over, under, or near the infant). These include pillows, including nursing pillows, comforters, quilts, sheepskins, bumper pads, positioners, and stuffed toys. Sleep clothing, such as a wearable blanket, can be used in place of blankets. Weighted blankets, weighted sleepers, weighted swaddles, or other weighted objects should not be placed on or near the sleeping infant.
- Offering a pacifier at bedtime and naptime is recommended. 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 firmly established. This is defined as having sufficient milk supply, con-

sistent, comfortable, and effective latch for milk transfer, and appropriate infant weight gain as defined by established normative growth curves. The time required to establish breastfeeding is variable.

- Parents should not smoke during pregnancy or after birth, and infants should not be exposed to secondhand smoke.
- Parents should avoid alcohol, marijuana, opioids, and illicit drug use during pregnancy and after birth.
- Avoid overheating and overbundling. The infant should be lightly clothed for sleep and the thermostat set at a comfortable temperature. The use of hats or other infant head coverings indoors is not recommended.
- Pregnant persons should obtain regular prenatal care, following guidelines for prenatal visits.
- Infants should be immunized in accordance with recommendations of the AAP and the CDC. There is no evidence that immunizations increase the risk of SIDS. Indeed, recent evidence suggests that immunizations may have a protective effect against SIDS.
- Avoid the use of commercial devices that are inconsistent with safe sleep recommendations. Devices advertised to maintain sleep position, “protect” a bed-sharing infant, or reduce the risk of rebreathing are not recommended because there is no evidence to support their safety or efficacy.
- Home cardiorespiratory and/or O₂ 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.
- Infants should have some time in the prone position (tummy time) while awake and observed. Alternating the placement of the infant’s head and orientation in the crib can also minimize the risk of head flattening from supine sleeping (positional plagiocephaly).
- Swaddling cannot be recommended as a strategy to reduce SIDS, as there is insufficient evidence. If infants are placed in a swaddle, it should be using a light blanket that is snug around the shoulders but looser around the hips to avoid hip dysplasia. Swaddled infants should always be placed supine, and once infants can roll to the prone or side position, all swaddling should be discontinued.
- Healthcare professionals, staff in newborn nurseries and NICUs, and childcare providers should adopt the SIDS reduction recommendations beginning at birth, or as soon as clinically able, to model safe sleep for caregivers.
- Media and manufacturers should follow safe sleep guidelines in their messaging, advertising, and social media.
- The national Safe to Sleep campaign should be continued with additional emphasis placed on strategies to increase breastfeeding while decreasing bed sharing and tobacco smoke exposure. The campaign should continue to have a special focus on the groups with higher rates of SIDS, including educational strategies tailored to individual racial-ethnic groups. Secondary care providers need to be targeted to receive these educational messages, including daycare providers, grandparents, foster parents, and babysitters. Efforts should also be made to introduce sleep recommendations before pregnancy and ideally in early education settings and school curricula to educate older siblings and teenage and adult babysitters and establish these practices as normative behavior. Research and surveillance should be continued on the risk factors, causes, and pathophysiologic 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.

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423.1 Sudden Unexpected Postnatal Collapse/Sudden Unexpected Early Neonatal Death

Sarah Vepraskas

Sudden unexplained postnatal collapse (SUPC) is a rare but potentially fatal event that occurs when a spontaneously breathing, previously healthy newborn suddenly becomes limp, pale, or cyanotic, bradycardic, unresponsive, apneic, and/or has cardiac and/or respiratory failure and requires cardiopulmonary resuscitation. SUPC results in death in about half of the infants and significant impairment in many survivors.

There is not a consensual definition for SUPC in the medical literature, although there is increasing awareness of SUPC as a clinical entity, with over 400 cases described. The most common definition of SUPC used is by the British Association of Perinatal Medicine and includes any term or near-term (defined as >35 weeks’ gestation) infant who meets the following criteria: (1) is well at birth (normal 5-minute Apgar and deemed well enough for routine care), (2) collapses unexpectedly in a state of cardiorespiratory extremis such that resuscitation with intermittent positive-pressure ventilation is required, (3) collapses within the first 7 days of life, and (4) either dies, goes on to require intensive care, or develops encephalopathy. A majority of reported events occur within 2 hours after birth, often at the time of the first breastfeeding attempt. Other potential medical conditions that place infants at higher risk, such as prematurity (<35 weeks’ gestation), perinatal asphyxia, sepsis, or congenital malformations, should be excluded before a diagnosis of SUPC is made.

Population-based studies estimate the incidence of SUPC to be 2.6–38 cases per 100,000 live births. The incidence varies widely because of the lack of both a definition consensus and standardized reporting system as well as differing inclusion and exclusion criteria. Furthermore, a consensus for coding SUPC has not been established, which likely also contributes to it being underreported.

The published estimations of SUPC are lower than what occur in the hospital and reflect only the critical events. When a defined time for the SUPC event is described, approximately one third of reported events occur during the first 2 hours, another one third between 2 and 24 hours, and another one third between 1 and 7 days after birth.

PATHOGENESIS

In most SUPC cases an underlying condition is never identified, although the literature suggests there is a variety of etiologies. Many of the events may be related to suffocation or entrapment, but it seems to have a complex pathophysiology that is poorly understood. One hypothesis is that the transition from fetal to extrauterine life could make the newborn more vulnerable during the first hour of life. During birth there is an initial surge of adenosine and prostaglandins, followed by a postnatal surge of catecholamines. A healthy newborn baby is aroused and awake after birth and starts continuous breathing movements. Shortly after birth, there is a rapid decrease in the inhibitory neuromodulator adenosine as the partial pressure of oxygen in the arterial blood rapidly increases and contributes to the increased activity in the newborn infant compared with the fetus. After the hormone surges, there is a period of diminished responsiveness to external stimuli and increased vagal tone; it is possible that autonomic instability could make infants vulnerable during this transitioning period.

It is also possible that impaired cardiorespiratory control resulting from hypoxic ischemic injury occurring days *before* birth could contribute to fatal cases of SUPC. Mild gliosis in brainstem areas involved in cardiorespiratory control was found at autopsy of seven infants with

SUPC. However, there are insufficient data to support an association between in utero hypoxic events and SUPC. Monogenic etiologies have not been explored to the same degree reported for SIDS in infants ≥ 2 months (see Table 423.4).

RISK FACTORS

Many reported SUPC cases occur while the infant is in the prone position, during skin-to-skin contact (SSC) with their mothers. SSC is traditionally defined as beginning at birth and lasting continually until the end of the first breastfeeding.

Additional risk factors for SUPC include the first breastfeeding attempt, cosleeping, a mother in the episiotomy position, a primiparous mother, and parents left alone with baby during the first hour after birth.

SSC and rooming-in have become common practice for healthy newborns and align with the Baby-Friendly Hospital Initiative (BFHI), a global program launched by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to encourage and recognize hospitals and birthing centers that promote the optimal level of care for infant feeding and mother/baby bonding. The BFHI recognizes and awards birthing facilities that successfully implement the "Ten Steps to Successful Breastfeeding," with step 4 being to initiate breastfeeding within 1 hour of birth and step 7 recommending the practice of rooming-in. The AAP clinical report on safe sleep and SSC in the newborn period both reviews the evidence supporting SSC and rooming-in during the newborn period and addresses the safety concerns and provides suggestions to improve safety after delivery. The literature supporting SSC also emphasizes the importance that mother and baby should not be left unattended during this early period.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of SUPC should be made only after other pathologic causes are excluded. One study consisting of 45 cases of unexpected collapse in newborns found that one third of infants had an underlying pathologic or clinical condition, such as sepsis, ductal-dependent congenital heart disease, congenital diaphragmatic hernia, intracranial hemorrhage, or a metabolic disorder. Additional etiologies to consider include airway obstruction, pneumonia, respiratory distress syndrome, hypoglycemia, vascular thrombosis or embolism, and pulmonary hypertension of the newborn. The differential diagnosis of SUPC is broad, and many conditions overlap with the differential diagnoses for BRUE (see Chapter 424), SUID, and SIDS.

For those infants who survive the event, testing to screen for an underlying pathology should be performed and tailored to the specific details of each case. A thorough history and physical exam should be performed before initiating the diagnostic workup to assist one in focusing the evaluation. Laboratory tests to consider include electrolytes; metabolic evaluation including glucose, ammonia, and lactate; an infectious evaluation including blood cultures, urinalysis, and urine cultures; and CSF analysis with CSF culture. Chest radiography, neuroimaging, echocardiogram, electrocardiogram, and comprehensive metabolic screening (included as part of the newborn screen in most states) could also be useful diagnostic tools. Postmortem examination in the case of death from presumed SUPC should be performed because underlying etiology of the event may be discovered during autopsy. In the event that no

identifiable etiology is discovered, next-generation gene testing for at-risk pathogenic variants should be performed (see Table 423.4).

OUTCOME

Approximately half of SUPC cases are thought to result in death, and there is remaining disability in most reported cases. A review of 17 and 45 SUPC cases in Germany and the United Kingdom showed a mortality rate of 42% and 27%, respectively. In the German study, almost two thirds of the surviving cases had neurologic deficits, and in the United Kingdom study, one third of infants either died or had residual neurologic deficits. Rates of death and neurologic abnormalities reported in the two aforementioned studies are comparable with other available case reports.

TREATMENT

Although there is no definitive treatment for infants who have suffered from SUPC, therapeutic hypothermia (TH) has been studied as a plausible therapy because 75% of newborns with no known cause for collapse develop a typical postasphyxia encephalopathy, evoking hypoxic-ischemic encephalopathy (HIE) (see Chapter 122.4). Given the low incidence, diversity of etiologies, uncertain pathophysiology, and underreporting, it would be difficult to perform an outcomes trial using TH for infants with SUPC. Case reports on outcomes using TH for SUPC infants report variable short-term outcomes; long-term data are lacking. In a sample of 22 infants who suffered SUPC and were treated in Portuguese hypothermia centers, a significant proportion had poor outcomes. In contrast, another case report of four patients with HIE and TH treatment after SUPC described three children as developmentally normal at 24-month follow-up and one child as having mild cerebral palsy.

PREVENTION

The known risk factors for SUPC can be used to aid in preventive efforts. Specifically, safety during SSC and rooming-in should be emphasized. Initiatives developed to standardize the procedure for immediate postnatal SSC have not proven to reduce the risk of SUPC. Frequent assessments of newborns should be performed, including observation of breathing, activity, color, tone, and position, to ensure they are in a position to avoid obstructive breathing or events leading to SUPC. It has also been suggested that continuous monitoring by trained staff members be done during SSC. However, that may be obtrusive to mother-infant bonding. Some have suggested continuous pulse oximetry during this period, but there is no evidence to support this practice, and this overmonitoring could lead to unnecessary parental concern. Because many cases of SUPC occur within the first few hours of life, the delivery unit should be staffed to permit frequent newborn assessments while preserving the developing mother-child bond.

Many of the same safety concerns that occur during SSC immediately after birth continue to be a concern during rooming-in if the mother is not given guidance on the safe rooming-in practices. Cosleeping should not be permitted on the postpartum unit. Mothers and families need to be informed of the risks of cosleeping. Staffing ratios should be determined to meet the needs of both mother and infant to allow for frequent assessments, rapid response time to call lights, and time for maternal education.

Chapter 424

Brief Resolved Unexplained Events and Other Acute Events in Infants

Amy M. DeLaroche and Joel S. Tieder

Infants may experience acute, self-resolving changes in their breathing, tone, mental status, and skin color. Usually these events are normal manifestations of developmental immaturity. Nonetheless, caregivers may worry that the acute event could have been life-threatening or is a sign of an undiagnosed medical problem and seek medical attention. In most cases, after a comprehensive history and physical examination, a clinician will determine the event to have been a benign or normal process, such as gastroesophageal reflux (GER) or periodic breathing of the newborn. At times, however, the event defies a simple explanation and drives uncertainty about risk from a serious underlying cause or a future event. This situation poses a diagnostic and management challenge for both the family and the clinician.

Historically, these events were feared as precursors to sudden infant death syndrome (SIDS) and were referred to as *near-miss SIDS*, *aborted crib deaths*, or *apparent life-threatening events* (ALTEs). These terms have been replaced because we now know that these events are not associated with SIDS and are rarely life-threatening. These terms were additionally problematic because they relied on the subjective interpretation of the caregiver, included a nonspecific constellation of symptoms, and did not distinguish well-appearing patients from those with symptoms.

Most of these acute events in infants are best described as brief resolved unexplained events (BRUEs). A BRUE is a diagnosis of exclusion and should be used only when the event is transient and remains unexplained after an appropriate medical evaluation.

DEFINITION

A BRUE (pronounced *brew*) is an event that occurs in an infant younger than 1 year that is described by the observer as a *sudden, brief, and resolved* episode that involved at least one of the following:

- Cyanosis or pallor
- Absent, decreased, or irregular breathing
- Marked change in tone, either hypertonia or hypotonia
- Altered level of responsiveness

The diagnosis of BRUE applies only to infants who were asymptomatic before the event and during the initial medical evaluation and when no explanation for the event is found through appropriate history and physical examination (Fig. 424.1).

Infants who experience a BRUE are categorized as either lower or higher risk for a subsequent event or a serious underlying disorder based on patient factors, characterization of the event, additional historical factors, and the physical examination.

A lower-risk infant is defined as:

- Age >60 days
- Gestational age ≥32 weeks and postconceptional age ≥45 weeks
- Occurrence of only 1 BRUE (no prior BRUE ever and not occurring in a cluster)
- Duration of event <1 minute
- No cardiopulmonary resuscitation (CPR) by trained medical provider required
- No concerning historical features
- No concerning physical examination finding

EPIDEMIOLOGY

The exact incidence of BRUEs is unknown, but BRUEs may account for up to 0.02% of pediatric emergency department visits. In a multicenter study of hospitals, 87% of patients met higher-risk criteria and 63% were hospitalized. Since the American Academy of Pediatrics published the Clinical Practice Guideline and introduced the term *BRUE*, hospitalizations have been decreasing, especially for lower-risk infants.

BRUEs are not precursors to SIDS. The incidence of mortality after a BRUE from an underlying cause is extremely low, as only 1 patient in a cohort of 2,036 patients died during a readmission after being evaluated for a BRUE. Overall, the risk of death among patients with a BRUE is estimated to approximate the baseline risk of death among infants in the first year of life.

For patients presenting with a BRUE, numerous risks must still be considered. First is the risk of an underlying diagnosis that could lead to serious morbidity or mortality if not diagnosed in a timely fashion. This is estimated to be 4% for patients presenting to the emergency department with a BRUE and includes a wide variety of illnesses, such as cardiac arrhythmias, infections, and brain injury. In one study of infants with a serious underlying diagnosis identified after evaluation for a BRUE, seizures were the most commonly identified diagnosis followed by airway abnormalities, abusive head trauma, bacterial or viral infections, and intussusception. Less common etiologies were arrhythmias, central apnea, and ingestions. These diagnoses may become evident in the emergency department, the inpatient service, outpatient follow-up, or on readmission to the hospital.

In contrast, it is more common for a benign explanation to be identified, with choking, reflux, breath-holding spells, acrocyanosis, colic, viral infections, dysphagia, and overfeeding noted in over half of patients diagnosed with a less serious explanation for the event (Table 424.1). Second is the risk of a recurrent event, which occurred in 2.7% of patients during their emergency department visit for a BRUE and in 18.2% of patients hospitalized for a BRUE. These events can be stressful for caregivers, particularly when the cause is unknown. Third is the risk that the caregivers become unnecessarily concerned about their healthy child. Clinicians should be aware of the challenges caregivers face when perceiving a threat of losing their child, there is medical uncertainty, or when their child is hospitalized. Recurrent events that occur during a period of observation can lead to better characterization and explanation of the event and, in some cases, may reassure caregivers. Fourth are the risks associated with medical care, such as nosocomial infections and inaccurate testing.

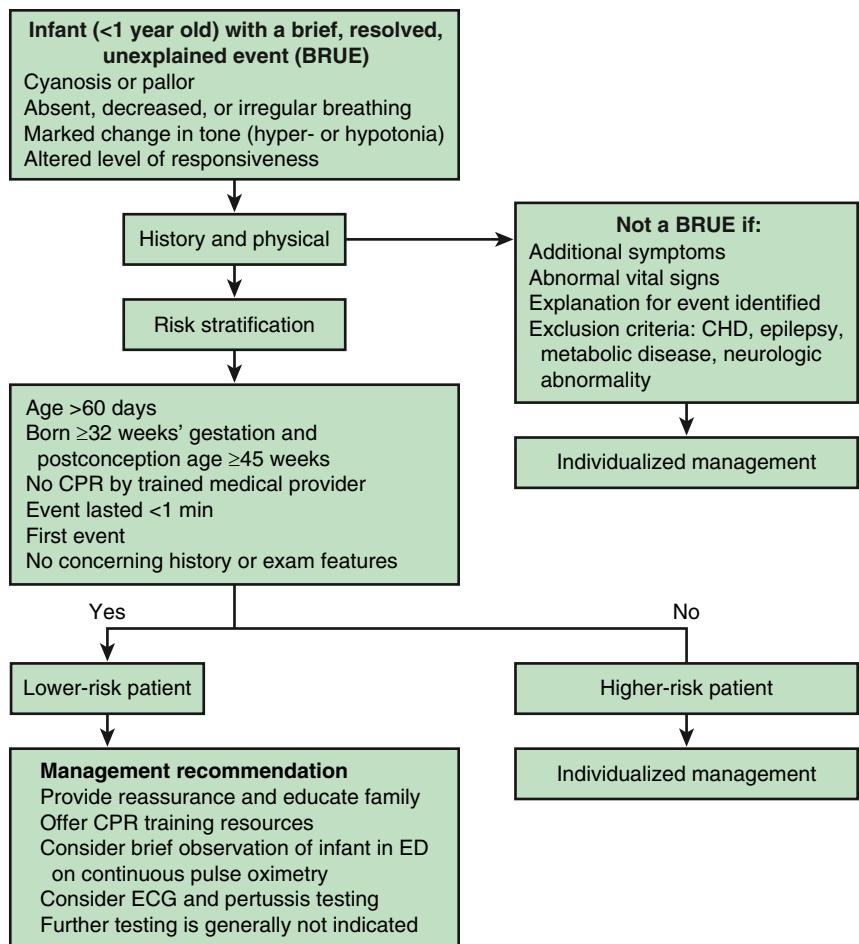
INITIAL HISTORY

An appropriate history and physical examination are key to evaluating an infant who has experienced an acute event (Table 424.2). Attention should be given to characterizing the event and interpreting the subjective experience of the caregiver to provide an objective description. The following questions can guide this process:

What was the infant doing before, during, and after the event? An event occurring during or after feeding will likely have a different explanation than one occurring during sleep or after crying. The sequence of events can also be diagnostic. A **breath-holding spell** begins with crying, followed by a period of apnea, perioral cyanosis, change of consciousness, and return to baseline.

Did the infant change color? It is often normal for infants to have blue discoloration (**perioral cyanosis or acrocyanosis**) around the lips or hands because of circulatory immaturity. Turning red or purple is also common when infants cry or become upset. The clinician's goal is to distinguish less concerning color change from **central cyanosis**, which is blue discoloration of the face, trunk, gums, or tongue that can indicate hypoxemia.

Did the infant experience central or obstructive apnea, or just choking or gagging? It is normal for infants to exhibit respiratory pauses of up to 20 seconds while awake and asleep. These can reflect **periodic breathing of the newborn** or normal REM sleep. Much more concerning are periods of no air movement that last longer than 20 seconds. **Obstructive apnea** results in paradoxical movement of the diaphragm and upper airway. In infants, this is most commonly caused by upper



and lower respiratory tract infections (e.g., bronchiolitis) and may precede the recognition of symptoms typically seen in viral respiratory infections. Infants also commonly gag or choke briefly during or shortly after feeds or with GER or vomiting. The resulting reflexive pause in respiration to protect the airway is sometimes referred to as **laryngospasm**. **Central apnea** is always concerning and occurs when the brainstem does not properly control the respiratory muscles. This may be seen in brain trauma from **nonaccidental trauma** and in rare disorders such as **congenital central hypoventilation syndrome**.

Was there a concerning change in muscle tone? Seizures in infants are concerning and difficult to diagnose, and they rarely present as typical seizure activity. They can present as staring spells, periods of episodic increased or decreased tone, or **infantile spasms**. It is normal for infants to have rapid jerking movements because of neurologic immaturity and infant reflexes (e.g., Moro, startle, and fencing reflex), and sometimes these can appear similar to seizures. One of the most serious and time-sensitive causes of seizures or central apnea is undiagnosed brain trauma from nonaccidental trauma, which may result in no other symptoms or physical examination findings upon presentation.

Was there an altered level of responsiveness? Episodic changes in consciousness and mental status can be difficult to assess in infants because of neurologic immaturity and variability in sleep-wake cycles. However, abrupt changes where the infant appears to lose consciousness after episodes of apnea or color change can be concerning for hypoxemia, hypoglycemia, or seizures.

Did the event self-resolve, or was an intervention required? Infants with choking from GER, vomit, or feeding difficulties generally improve spontaneously or with help clearing the airway. A serious underlying cause is more likely if CPR was indicated and then provided, though this may be difficult to assess if no medically trained individuals witnessed the event.

Additional History

A careful, detailed history can lead to an explanation; the key elements are summarized in **Tables 424.1 and 424.2**. A clinician should inquire about other symptoms (e.g., fever, upper respiratory infection [URI] symptoms, spitting up). A history of breathing problems, prenatal or perinatal concerns, prematurity, and growth and developmental problems is important. Premature infants, particularly those still under 43 weeks corrected gestational age, are at higher risk for underlying causes, such as apnea of prematurity. A careful feeding history can detect oropharyngeal dysphagia or GER-related problems (i.e., laryngospasm).

A targeted family history can reveal risk for sudden death, cardiac arrhythmias, and metabolic, genetic, and neurologic disease. A social history, particularly by someone trained to detect nonaccidental trauma, can reveal recent trauma, prior child welfare involvement, substance abuse, poisoning or misuse of medications, and environmental exposures (e.g., secondhand tobacco smoke and mold). It is important to understand who observed the event, who normally takes care of the infant, and if there are any discrepancies in the explanation of the event.

Consider infectious exposures. Infants exposed to underimmunized family members are at risk for pertussis. Respiratory syncytial virus (RSV) and other respiratory viruses, as well as pertussis, can present with apnea before the onset of URI symptoms.

Physical Examination

A careful physical examination may reveal a causative or underlying diagnosis. Abnormal growth and head circumference may reflect feeding, developmental, and neurologic problems. Abnormal vital signs and pulse oximetry can suggest infectious, cardiac, and neurologic abnormalities. A careful skin and mouth examination can reveal subtle signs. For example, child abuse should be suspected in infants with bruises, petechiae, or a torn frenulum. Signs of airway abnormalities,

Table 424.1

Symptom-Based Approach to BRUEs: Other Conditions that Might Be Confused with a BRUE

DIAGNOSTIC CATEGORIES	EXPLANATORY CAUSES TO CONSIDER	SUGGESTIVE HISTORICAL FINDINGS	SUGGESTIVE PHYSICAL EXAMINATION FINDINGS	TESTING TO CONSIDER
Gastrointestinal	GER Intussusception Volvulus Oropharyngeal dysphagia	Coughing, vomiting, choking, gasping temporally related to feeds or regurgitation of gastric contents Feeding difficulties Recent preceding feed Irritability after feeds Milk in mouth/nose Bilious emesis Pulling legs to chest Bloody/mucousy stool Lethargy after event	Gastric contents in the nose and mouth Choking, gagging, or oxygen desaturation temporally related to feeding or regurgitation of gastric contents	Upper GI to assess for anatomic anomalies Clinical swallow evaluation Abdominal ultrasound pH probe
Infectious	Upper and lower respiratory tract infection (RSV, pertussis, pneumonia) Bacteremia Meningitis Urinary tract infection	Preceding URI symptoms Multiple events on the day of presentation Sick exposures Foul-smelling urine	Fever/hypothermia Lethargy Ill appearance Coryza Cough Wheeze Tachypnea	NP swab for RSV, pertussis Chest radiograph CBC and blood culture Cerebrospinal fluid analysis and culture Urinalysis and culture
Neurologic	Seizures Breath-holding spells Congenital central hypoventilation syndrome Neuromuscular disorders Congenital malformations of the brain and brainstem Malignancy Intracranial hemorrhage	Multiple events Loss of consciousness Change in tone Abnormal muscular movements Eye deviation Preceding triggers	Papilledema Abnormal muscular movements Hypertonicity or flaccidity Abnormal reflexes Microcephaly or macrocephaly Dysmorphic features Signs of trauma or poisoning (see "Child maltreatment" below)	EEG Neuroimaging
Respiratory/ENT	Apnea of prematurity Apnea of infancy Periodic breathing Airway anomaly Aspiration Foreign body Obstructive sleep apnea	Prematurity Foreign body Aspiration Noisy breathing	Wheezing Stridor Crackles Rhonchi Tachypnea	Chest radiograph Neck radiograph Laryngoscopy Bronchoscopy Esophagoscopy Polysomnography
Child maltreatment	Nonaccidental head trauma Smothering Poisoning Factitious syndrome imposed on another (formerly Munchausen syndrome by proxy)	Multiple events Unexplained vomiting or irritability Recurrent BRUEs Historical discrepancies Family history of unexplained death, SIDS, or BRUEs Single witness of event Delay in seeking care	Bruising (especially in a nonmobile child) Ear trauma, hemotympanum Acute abdomen Painful extremities Oral bleeding/trauma Frenulum tears Unexplained irritability Retinal hemorrhages Depressed mental status	Skeletal survey CT/MRI of the head Dilated funduscopic examination if head imaging concerning for trauma Toxicology screen Social work evaluation
Cardiac	Dysrhythmia (prolonged QT syndrome, Wolff-Parkinson-White syndrome) Cardiomyopathy Congenital heart disease Myocarditis	Feeding difficulties Growth difficulties Diaphoresis Prematurity	Abnormal heart rate/rhythm Murmur Decreased femoral pulses	Four-extremity blood pressure Preductal and postductal oxygen saturation measurements ECG Echocardiogram Serum electrolytes, calcium, magnesium
Metabolic/genetic	Hypoglycemia Inborn errors of metabolism Electrolyte abnormalities Genetic syndromes including those with craniofacial malformations	Severe initial event Multiple events Event associated with period of stress or fasting Developmental delay Associated anomalies Growth difficulties Severe/frequent illnesses Family history of BRUE, consanguinity, seizure disorder, or SIDS	Dysmorphic features Microcephaly Hepatomegaly	Serum electrolytes; glucose, calcium, and magnesium levels Lactate Ammonia Pyruvate Urine organic and serum amino acids Newborn screen

BRUE, Brief resolved unexplained event; ECG, electrocardiogram; EEG, electroencephalogram; ENT, ear, nose, and throat; GER, gastroesophageal reflux; GI, gastrointestinal; NP, nasopharyngeal; RSV, respiratory syncytial virus; SIDS, sudden infant death syndrome; URI, upper respiratory infection.

From Kliegman RK, Lye PS, Bordoni BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*. Philadelphia: Elsevier; 2018: Table 5.3.

Table 424.2 Important Historical Features of a BRUE

PREEVENT	
Condition of child	Awake vs asleep
Location of child	Prone vs supine, flat or upright, in crib/car seat, with pillows, blankets
Activity	Feeding, crying, sleeping
EVENT	
Respiratory effort	None, shallow, gasping, increased Duration of respiratory pauses
Color	Pallor, red, cyanotic Peripheral, whole body, circumoral, lighting of room
Tone/movement	Rigid, tonic-clonic, decreased, floppy Focal vs diffuse Ability to suppress movements
Level of consciousness	Alert, interactive, sleepy, nonresponsive
Duration	Time until normal breathing, normal tone, normal behavior Detailed history of caregiver actions during event to aid in defining time course
Associated symptoms	Vomiting, sputum production, blood in mouth/nose, eye rolling
POSTEVENT	
Condition	Back to baseline, sleepy, postictal, crying If altered after event, duration of time until back to baseline
INTERVENTIONS	
What was performed	Gentle stimulation, blowing in face, mouth-to-mouth, cardiopulmonary resuscitation
Who performed intervention	Medical professional vs caregiver
Response to intervention	Resolution of event vs self-resolving
Duration of intervention	How long was intervention performed
MEDICAL HISTORY	
History of present illness	Preceding illnesses, fever, rash, irritability, sick contacts
Medical history	Prematurity, prenatal exposures, gestational age, birth trauma Noisy breathing since birth Any medical problems, prior medical conditions, prior hospitalizations Developmental delay Medications
Feeding history	Gagging, coughing with feeds, poor weight gain
Family history	Neurologic problems Cardiac arrhythmias Sudden death, childhood deaths, BRUEs Neonatal problems Consanguinity
Social history	Home situation Caregivers Smoke exposure Medications in the home

BRUE, Brief resolved unexplained event.

From Kliegman RK, Lye PS, Bordoni BJ, et al., eds. *Nelson Pediatric Symptom-Based Diagnosis*. Philadelphia: Elsevier; 2018: Table 5.4.

such as inspiratory or expiratory stridor or stertor, can lead to a diagnosis of respiratory infections, vascular rings, hemangioma, laryngomalacia, tracheomalacia, or facial dysmorphism.

Testing

In the past, it was common for clinicians to routinely test infants presenting with such events using complete blood counts (CBCs), appropriate cultures, and GER testing. However, it is known that these tests are unlikely to reveal a cause and even more likely to lead to a false-positive result. False positives can, in turn, contribute to missed diagnoses, additional unnecessary testing, patient harm, greater parental concern, and increased costs.

In lower-risk infants, routine laboratory testing and diagnostic imaging (CBC, bacterial cultures, blood gas and glucose, metabolic panels, urinalysis, GER testing, chest radiograph, neuroimaging, electroencephalogram [EEG], sleep study) is *not recommended*. *The few situations where testing may be considered in the lower-risk population include:*

- Pertussis testing in underimmunized or exposed individuals.
- ECG may reveal a prolonged QTc syndrome if there is a concerning family history, but routine testing is not indicated.
- Rapid viral testing can help diagnose subclinical viral causes, but these tests can be positive from recent past infections that may not be the cause of the concerning event.
- A brief period of continuous pulse oximetry and serial observations to detect hypoxemia and apnea.

In higher-risk infants, routine screening tests may not be needed. Testing should be done because of concerns from the history and physical or to further characterize repeat BRUEs.

- Continuous pulse oximetry or cardiorespiratory monitoring under a period of observation may help characterize repeat events.
- A swallow evaluation by a trained feeding expert might reveal oropharyngeal dysphagia in premature or young infants.
- Head imaging with CT or MRI is indicated when there is suspicion of nonaccidental trauma because of bruising in nonambulatory infants, concerning bruising patterns, history of unexplained death in a sibling, or inconsistent history of the event.
- Neurology consult or EEG or head imaging may lead to a diagnosis of epilepsy if there is a concern for seizure. However, it is reasonable to perform this consultation and testing as an outpatient in well-appearing infants.
- Otolaryngology consultation to detect anatomic disorders of the airway (e.g., laryngomalacia, tracheomalacia, and tracheoesophageal fistula).
- Pulmonary/sleep medicine consultation to detect disordered breathing (e.g., central apnea and obstructive sleep apnea).

Management

Although the value of hospital admission is debatable, lower-risk infants are much less likely to benefit from admission compared to higher-risk infants. Nationally, there is a trend away from routine admission for all BRUE patients, particularly those meeting lower-risk BRUE criteria. For all BRUEs, it is uncommon for a hospital admission to lead to a diagnosis of a serious underlying disorder. Sometimes, however, a longer period of observation than is practical in a clinic or emergency department can help characterize repeat events, should they recur, and reduce the uncertainty of a recurrent event for caregivers. Additional benefits of hospitalization include serial assessments of feeding, breathing, sleep, and social patterns. *The decision for hospital admission should incorporate the needs and preferences of the family and patient and the ability to follow up closely with a primary care physician.* In weighing the risks and benefits of this decision, it is important to recognize that hospitalization can unnecessarily increase stress for the family and patient through false alarms and iatrogenic complications. CPR education should be considered for all families. Home apnea monitoring should not be done. Close outpatient follow-up with a primary care physician is important, as almost half of serious underlying diagnoses are not identified during the first visit for a BRUE.

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Section 2

Disorders of the Respiratory Tract

Chapter 425

Congenital Disorders of the Nose

Joseph Haddad Jr.

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. 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. Acquired nasal congestion with obstruction is common in the first year 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 first 6 months 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 421).

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 A (IgA), 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 minutes. Estimates of daily mucus production vary from 0.1 to 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 (*arrhinia*), 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 31). Rarely, the alae nasi are sufficiently thin and poorly supported, resulting 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 buccopharyngeal 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 [see later], 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.

CHARGE syndrome (coloboma, heart disease, atresia or stenosis of the choanae, retarded growth and development or central nervous system [CNS] anomalies or both, genital anomalies or hypogonadism or both, and ear [external, middle, inner 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. The CNS involvement (~90%) includes reduced function of cranial nerves I, V, VII, VIII, IX, and X, as well as vision and hearing deficits. Most (~90%) patients with CHARGE syndrome have autosomal dominant de novo pathogenic variants in the *CHD7* gene, which is involved in chromatin organization. Immunologic deficiencies may be noted that overlap with the 22q11.2 deletion syndrome.

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 can breathe through their mouths at once have trouble when sucking and swallowing, becoming cyanotic when they attempt to feed.

Diagnosis

The 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. 425.1).

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, although a large meta-analysis demonstrated that there is no benefit to stenting. Another option is a transpalatal repair, and this is done when a transnasal endoscope cannot be placed through the nose because of

thick bony atresia 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, although its efficacy is questionable.

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 cannulas 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.

Congenital isolated absence of a membranous nasal septum has also been reported.

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, hypopituitarism, and cardiac and urogenital malformations. Diagnosis is made by CT of the nose (Fig. 425.2) with a pyriform aperture width less than ~11 mm. Medical management (nasal decongestants, humidification, nasopharyngeal airway insertion, management of reflux) is typically attempted for about 2 weeks; if the child still cannot feed or breathe without difficulty, then surgical repair by means of an anterior, sublabial approach may be needed. 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 intracranially with 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

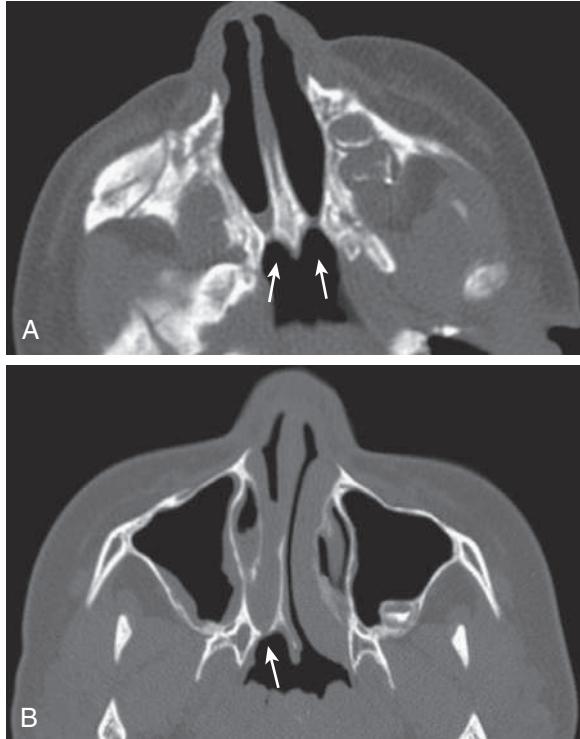


Fig. 425.1 Choanal atresia. A, Axial CT image in a 1-day-old neonate with severe respiratory distress shows bilateral bony choanal atresia with retained fluid in the right nasal cavity, medial bowing of the lateral nasal wall, and a thickened vomer (arrows). B, Axial CT image in a 12-yr-old child with chronic nasal obstruction and purulent rhinorrhea shows unilateral (right) bony atresia with fluid in the nasal cavity (arrow). (From Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 12th ed. Philadelphia: Saunders; 2013: Fig. 8.13.)

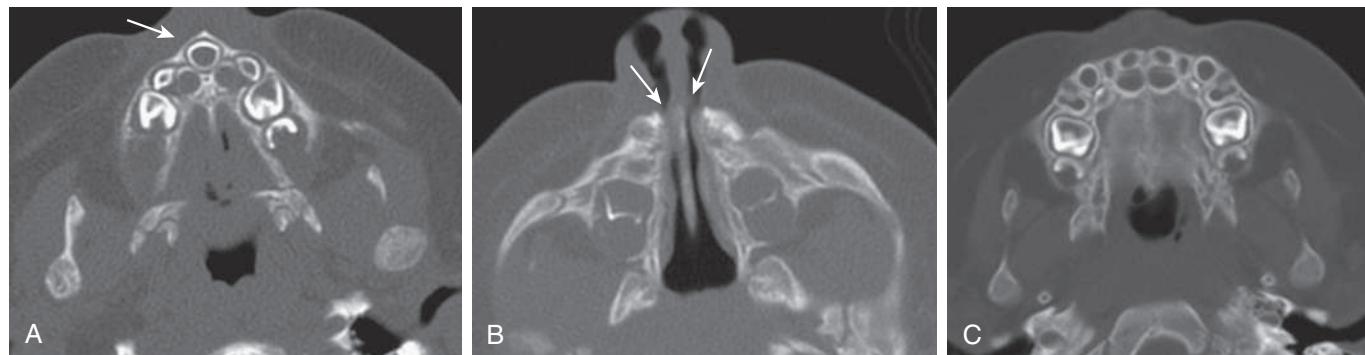


Fig. 425.2 Congenital nasal pyriform aperture stenosis in a 1½-mo-old infant with episodes of respiratory distress during breastfeeding. A, Axial CT image shows a triangular hard palate and solitary central maxillary mega-incisor (arrow). B, An axial CT image shows narrowing of the anterior and inferior nasal passages (arrows). C, Normal infant maxilla for comparison. (From Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 12th ed. Philadelphia: Saunders; 2013: Fig. 8.14.)



Fig. 425.3 Nasal dermoid manifesting as a midline sinus opening. (From Elluru RG. Congenital and acquired malformations of the nose and nasopharynx. In: Lesperance MM, ed. Cummings Pediatric Otolaryngology, 2nd ed. Philadelphia: Elsevier; 2022: Fig. 5.5, p. 67.)

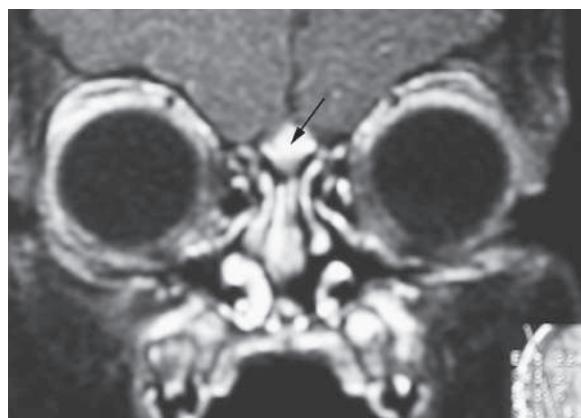


Fig. 425.4 Coronal CT scan of nasal dermoid with intracranial extension (arrow). (From Manning SC, Bloom DC, Perkins JA, et al. Diagnostic and surgical challenges in the pediatric skull base. Otolaryngol Clin North Am. 2005;38:773–794, Fig. 2.)

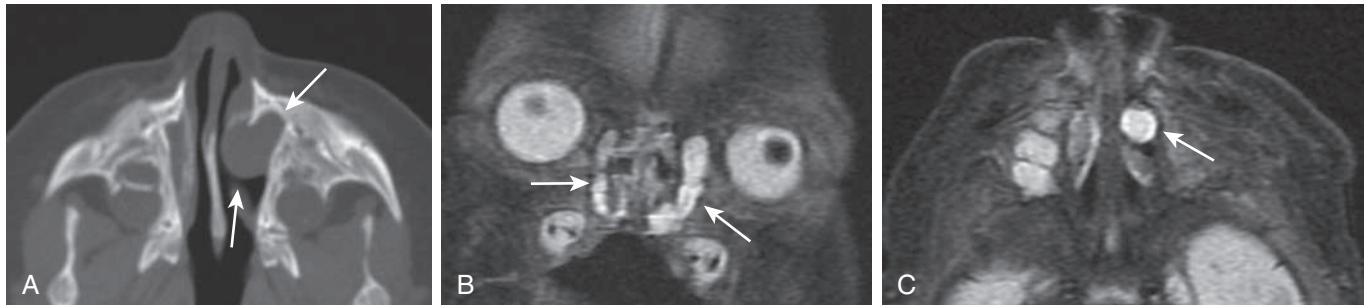


Fig. 425.5 Congenital nasolacrimal duct mucoceles in a 1-day-old neonate. A, Axial CT image shows a left nasal round soft tissue mass with enlargement of the ipsilateral nasolacrimal duct and canal (arrows). B and C, Coronal and axial fast spin echo inversion recovery MR images show bilateral cystic enlargement of the nasolacrimal sacs and ducts (arrows). (From Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 12th ed. Philadelphia: Saunders; 2013: Fig. 8.15, p. 78.)

type of congenital midline nasal mass and have been reported to represent up to 61% of lesions. Nasal dermoids are firm, noncompressible, and painless and often have a dimple or pit on the nasal dorsum (sometimes with hair being present) (Fig. 425.3). They can predispose to intracranial infections if an intracranial fistula or sinus is present, although recurrent infection of the dermoid itself is more common; given the risk for serious infection, surgical excision is always indicated for nasal dermoids. 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 magnetic resonance imaging (MRI) is also helpful because of its superior ability to define intracranial extension (Fig. 425.4). Surgical excision of these masses is generally required, with the extent and surgical approach based on the type and size of the mass.

Encephaloceles may be *sincipital* (nasofrontal, nasoethmoidal, naso-orbital) or *basal* (transtethmoidal, sphenoethmoidal, transsphenoidal, spheno-orbital); presentations include a glabellar or nasal mass, nasal obstruction, hypertelorism, and orbital/visual changes.

Other nasal masses include *hemangiomas*, *congenital nasolacrimal duct obstruction* (which can occur as an intranasal mass) (Fig. 425.5), nasal polyps, and tumors such as rhabdomyosarcoma (see Chapter 549). Nasal polyps are rarely present at birth, but the other masses often present at birth or in early infancy (see Chapter 427).

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 57).

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, primarily CT scan. In the case of surgically correctable congenital problems such as choanal atresia, surgery is performed after the child is deemed healthy and free of life-threatening problems such as congenital heart disease.

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Chapter 426

Acquired Disorders of the Nose

Joseph Haddad Jr. and Sonam N. Dodhia

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 also 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 *mucocoeles 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.

426.1 Nasal Foreign Bodies

Joseph Haddad Jr. and Sonam N. Dodhia

ETIOLOGY

Foreign bodies (food, beads, crayons, small toys, erasers, paper wads, buttons, batteries, beans, stones, pieces of sponge or capsule sponge toys, and other small objects) are often placed in the nose by young or developmentally delayed children and constitute $\leq 1\%$ of pediatric emergency department visits. Nasal foreign bodies can go unrecognized for long periods 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%). Irrigation results in mucosal swelling because some foreign bodies are hygroscopic 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 be visualized; 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 or if foreign body is suspected but physical exam with sinus endoscopy or anterior rhinoscopy is negative.

TREATMENT

An initial 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 extrication of the foreign body. Prompt removal minimizes the danger of aspiration and local tissue necrosis, and this can usually be performed with the aid of topical anesthesia, with forceps or nasal suction. Common noninvasive

techniques include simple nose blowing and the “mother’s kiss” technique. The “mother’s 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. Other non-invasive options include blowing air into a drinking straw in a child’s mouth and applying high-flow oxygen (10–15 L/min) to the unaffected nostril. 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. 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. Age (>5) and disk-shaped foreign body are predictors for operating room removal of foreign body.

COMPLICATIONS

Serious complications include posterior dislodgement 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 or saddle nose. 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 257). Toxic shock syndrome is also rare and most commonly occurs from nasal surgical packing (see Chapter 227.2); oral antibiotics should be administered when nasal surgical packing is placed.

PREVENTION

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

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426.2 Epistaxis

Joseph Haddad Jr. and Sonam N. Dodhia

Although rare in infancy, nosebleeds are common in children between the ages of 3 and 8, then decline in incidence after puberty. They are also more common during winter months. 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 and the anterior location make it prone to exposure to dry air and trauma.

ETIOLOGY

Epistaxis can be classified as primary (idiopathic; majority of cases) or secondary based on cause, and this has implications for diagnosis and management. Common causes of secondary nosebleeds from the anterior septum include digital trauma, foreign bodies, dry air, and inflammation, including upper respiratory tract

infections, sinusitis, and allergic rhinitis (Table 426.1). 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* (HHT) (see Chapter 481.3), varicosities, hemangiomas, and in children with thrombocytopenia, deficiency of clotting factors, particularly von Willebrand disease (see Chapter 526), hypertension, renal failure, or venous congestion. Screening for HHT is recommended for patients with obvious nasal/oral telangiectasias and those with a personal or familial history of recurrent nosebleeds. Recurrent epistaxis despite cauterization 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, unilateral nosebleeds may be the initial presenting symptom in **juvenile nasal angiofibroma**, which occurs in adolescent males.

CLINICAL MANIFESTATIONS

Epistaxis usually occurs without warning, with blood flowing slowly but freely from one 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 (lower third of the nose) should be compressed for 5 minutes, 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 oxy-metazoline (Afrin) or phenylephrine (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 cauterity with silver nitrate may prevent further difficulties. Because the septal cartilage derives its nutrition from the overlying mucoperichondrium, only one 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. Ointments prevent infection, increase moisture, decrease bleeding, and are commonly used in clinical practice. 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 Kieselbach plexus. For those with recurrent epistaxis, there may be short-term benefits to using bipolar electrocautery over silver nitrate chemical cauterity, although treatments were equivocal after 2 years. 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 525). 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-year-old and in 30- to 40-year-olds, but the incidence peaks in adolescent and preadolescent boys. CT with contrast medium enhancement and magnetic resonance imaging (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 help 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.

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Table 426.1 Possible Causes of Epistaxis

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

From Kucik CJ, Clenney T. Management of epistaxis. Am Fam Physician. 2005;71(2):305–311.

Chapter 427

Nasal Polyps

Joseph Haddad Jr.

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 1% and 4% of the population will develop nasal polyps at some point; 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 454) 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 years old with nasal polyps, even in the absence of typical respiratory and digestive symptoms. Nasal polyposis is also associated with chronic sinusitis (see Chapter 429) and allergic rhinitis. Large population studies have noted a significant familial risk in having chronic rhinosinusitis with polyposis. In the *Samter triad*, nasal polyps are associated with aspirin sensitivity and asthma; this condition is rare in children.

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, grapelike masses squeezed between the nasal turbinates and the septum.

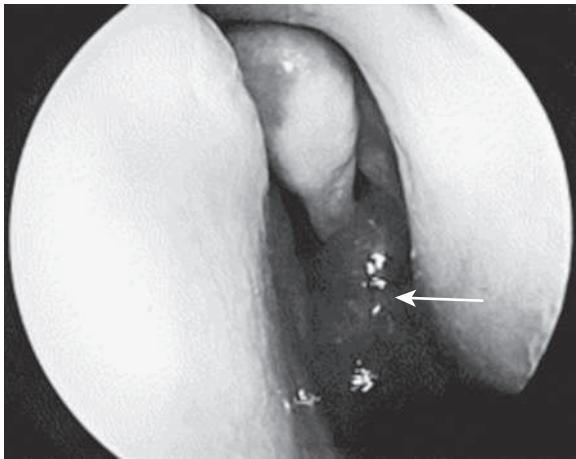


Fig. 427.1 Antrochoanal polyp viewed endoscopically (arrow). (From Basak S, Karaman CZ, Akdilli A, et al. Surgical approaches to antrochoanal polyps in children. *Int J Pediatr Otorhinolaryngol*. 1998;46:197–205.)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Examination of the external nose and rhinoscopy should be performed. Ethmoidal polyps can be readily distinguished from the well-vascularized turbinate tissue, which is pink or red; antrochoanal polyps may have a fleshier appearance (Fig. 427.1). 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. 427.2).

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 appear to result in nasal symptom improvement but were found to have no effect on those with CF. Dupilumab inhibits interleukin (IL)-4 and IL-13, proinflammatory cytokines involved in polyp formation, and is approved in patients ≥18 years of age for the treatment of chronic rhinosinusitis with nasal polyps.

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, typically via endoscopic sinus surgery, or, alternatively, with a mini-Caldwell procedure. 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.

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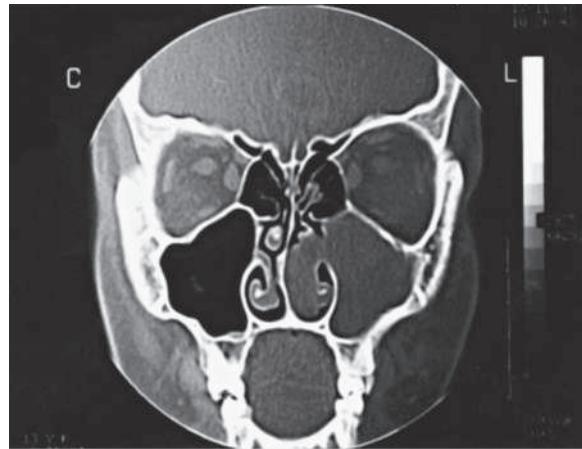


Fig. 427.2 A typical CT image of an isolated antrochoanal polyp on the left side. (From Basak S, Karaman CZ, Akdilli A, et al. Surgical approaches to antrochoanal polyps in children. *Int J Pediatr Otorhinolaryngol*. 1998;46:197–205.)

Chapter 428

The Common Cold

Katherine M. Richardson and Jennifer E. Schuster

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 310), but the syndrome can be caused by many different virus families (Table 428.1). Human rhinoviruses (HRVs) 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 307), human metapneumovirus (MPV; see Chapter 308), parainfluenza viruses (PIVs; see Chapter 306), seasonal coronaviruses (see Chapter 311), and adenoviruses (see Chapter 309). Common cold symptoms may also be caused by influenza viruses and nonpolio enteroviruses. 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 HRV infection occurs in the early fall (August–October) and in the late spring (April–May); however, HRVs are typically detected year-round. Historically, the seasonal incidence for PIV usually peaks in the summer, fall, and late spring and is highest between December and April for RSV, influenza viruses, MPV, 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 six to eight colds per year, but 10–15% of children have at least 12 infections per year. The incidence of illness decreases with increasing age, with two to three 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 first year 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, and in fact many children in daycare have asymptomatic viral infections. However, the incidence of illness remains higher in the daycare group through at least the first 3 years 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 three mechanisms: direct hand contact (self-inoculation of one's own nasal mucosa or conjunctivae 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 HRV 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 HRV 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 change the antigens presented on the surface of the virus because of genetic drift and thus behave as though there were multiple viral serotypes. The interaction of coronaviruses (see Chapter 311) 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, with possibility for some cross protection between different coronaviruses. There are four types of PIV, two antigenic subgroups of RSV, and four genotypes of MPV. In addition to antigenic diversity, many of these viruses are able to reinfect the upper airway because mucosal immunoglobulin A (IgA) induced by previous infection is short lived, and the brief incubation period of these viruses allows the establishment of infection before immune memory is able to respond. Although reinfection is not completely prevented by the adaptive host response to these viruses, the severity of illness is moderated by preexisting immunity.

Table 428.1 Pathogens* Associated with the Common Cold

ASSOCIATION	PATHOGEN	RELATIVE FREQUENCY**	OTHER COMMON SYMPTOMS AND SIGNS
Agents primarily associated with the common cold	Rhinoviruses Coronaviruses, including SARS-CoV-2 variants	Frequent Frequent	Wheezing/bronchiolitis
Agents primarily associated with other clinical syndromes that also cause common cold symptoms	Respiratory syncytial virus Human metapneumovirus Bocavirus Influenza viruses Parainfluenza viruses Adenoviruses Enteroviruses Coxsackievirus A Other nonpolio enteroviruses	Occasional Occasional Occasional Uncommon Uncommon Uncommon Uncommon	Bronchiolitis in children <2yr of age Pneumonia and bronchiolitis Uncertain role Influenza-like illness, pneumonia, croup Croup, bronchiolitis Pharyngoconjunctival fever (palpebral conjunctivitis, watery eye discharge, pharyngeal erythema) Herpangina (fever and ulcerated papules on posterior oropharynx) Aseptic meningitis

*It is not unusual to have one or more respiratory pathogens.

**Relative frequency of colds caused by the agent.

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 HRV, coronaviruses, 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, such as interleukin-8, that attract polymorphonuclear cells into the nasal submucosa and epithelium 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, rather than direct damage to the respiratory tract by the virus. 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 3 weeks in the otherwise recovering healthy host. Inflammation can obstruct the sinus ostia or eustachian tube, predisposing to bacterial sinusitis or otitis media, respectively.

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 second and third 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 weeks after resolution of other symptoms. Influenza viruses, RSV, MPV, and adenoviruses are more likely than HRV or coronaviruses to be associated with fever and other constitutional symptoms, and HRV is more commonly associated with wheezing, particularly in older children. 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 week, although 10% last for 2 weeks.

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 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 and other upper respiratory tract infections (Table 428.2).

LABORATORY FINDINGS

Routine laboratory studies are not helpful for the diagnosis and management of the common cold. A nasal smear for eosinophils (Hansel stain) may be useful if allergic rhinitis is suspected (see Chapter 184). 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 (PCR), culture, antigen detection, or serologic methods. These studies are generally not indicated in patients with colds, because a specific etiologic diagnosis is useful

Table 428.2 Conditions that Can Mimic the Common Cold

CONDITION	DIFFERENTIATING FEATURES
Allergic rhinitis	Prominent itching and sneezing, nasal eosinophils; Hansel stain can aid diagnosis
Vasomotor rhinitis	May be triggered by irritants, weather changes, spicy foods, etc.
Rhinitis medicamentosa	History of nasal decongestant use
Foreign body	Unilateral, foul-smelling secretions Bloody nasal secretions
Sinusitis	Presence of fever, headache or facial pain, or periorbital edema or persistence of rhinorrhea or cough for longer than 10–14 days
Streptococcosis	Mucopurulent nasal discharge that excoriates the nares, no cough
Pertussis	Onset of persistent or severe paroxysmal cough
Congenital syphilis	Persistent rhinorrhea with onset in the first 3 mo of life

only when treatment with an antiviral agent is contemplated, such as for influenza viruses. Bacterial cultures, PCR, or antigen detection are useful only when group A streptococcus (see Chapter 229) or *Bordetella pertussis* (see Chapter 243) is suspected. The isolation of 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.

Antiviral Treatment

Specific antiviral therapy is not available for HRV infections. The neuraminidase inhibitors oseltamivir, zanamivir, and peramivir, as well as polymerase acidic endonuclease inhibitor baloxavir marboxil, have a modest effect on the duration of symptoms associated with influenza viral infections in children. The difficulty of distinguishing influenza from other common cold pathogens and the necessity that therapy be started early in the illness (within 48 hours 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 prevent dehydration and to thin secretions and soothe respiratory mucosa. The common home remedy of ingesting warm fluids may soothe mucosa, increase nasal mucus flow, or loosen respiratory secretions. Topical nasal saline may temporarily remove secretions, and saline nasal irrigation may reduce symptoms. Cool, humidified air has not been well studied but may loosen nasal secretions; however, cool-mist humidifiers and vaporizers must be cleaned after each use. The World Health Organization suggests that neither steam nor cool-mist therapy be used in treatment of a cold.

The use of oral nonprescription therapies (often containing antihistamines, antitussives, and decongestants) for cold symptoms in children is controversial. Although some of these medications are effective in adults, no study demonstrates a significant effect

in children, and there may be serious side effects. Young children cannot participate in the assessment of symptom severity, so studies of these treatments in children have generally been based on observations by parents or other observers, a method that is likely to be insensitive for detection of treatment effects. Because of the lack of direct evidence for effectiveness and the potential for unwanted side effects, it is recommended that nonprescription cough and cold products not be used for infants and children younger than 4 years of age. A decision whether to use these medications in older children must consider the likelihood of clinical benefit compared with the potential adverse effects of these drugs. The prominent or most bothersome symptoms of colds vary in the course of the illness. If symptomatic treatments are used, it is reasonable to target therapy to specific bothersome symptoms, and care should be taken to ensure that caregivers understand the intended effect and can determine the proper dosage of the medications. It is also important to instruct caregivers to read labels carefully in case multiple medications are present in one formula to avoid overdose.

Zinc, given as oral lozenges to previously healthy patients, reduces the duration but not the severity of symptoms of a common cold if begun within 24 hours of symptoms. The function of the HRV 3C protease, an essential enzyme for HRV replication, is inhibited by zinc, but there has been no evidence of an antiviral effect of zinc *in vivo*. The effect of zinc on symptoms has been inconsistent, with some studies reporting dramatic treatment effects (in adults), whereas other studies find no benefit. Side effects are common and include decreased taste, bad taste, and nausea.

Fever

Fever is not usually associated with an uncomplicated common cold, and antipyretic treatment is generally not indicated. Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease discomfort from cold-related headache or myalgias.

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 years 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. Pseudoephedrine may be more effective than phenylephrine as an oral agent to treat nasal congestion—its benefit seems to be greatest in the first day of treatment; after this it does not show much benefit over placebo. Aromatic vapors (such as menthol) for external rub may improve the 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 HRV 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 305). NSAIDs are somewhat effective in relieving discomfort caused by a cold, but there is no clear evidence of an effect on respiratory symptoms.

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 years). Honey has a modest effect on relieving nocturnal cough and is unlikely to be harmful in children older than 1 year of age. Honey should be avoided in children younger than 1 year of age because of the risk for botulism (see Chapter 237).

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. Dextromethorphan hydrobromide has no effect on cough from colds and has potential enhanced toxicity. Expectorants such as guaifenesin are not effective antitussive agents.

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 680), 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 of the common cold symptoms has no effect on the subsequent development of AOM, which can be viral or bacterial.

Sinusitis is another complication of the common cold (see Chapter 429). 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 5–9% 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 acute symptoms worsen over time; or if acute 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; however, both RSV and HRV have been implicated in pneumonia, especially in developing and emerging countries.

Exacerbation of **asthma** is a potentially serious complication of colds. The majority of asthma exacerbations in children are associated with common cold viruses. 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.

PREVENTION

Chemoprophylaxis or immunoprophylaxis is generally not available for the common cold. Immunization or chemoprophylaxis against influenza can prevent colds caused by this pathogen, but influenza is responsible for only a small proportion of all colds. Palivizumab is recommended to prevent severe 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. Zinc sulfate taken for a minimum of 5 months 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 HRV followed by self-inoculation may be prevented by frequent handwashing 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.

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Chapter 429

Sinusitis

Diane E. Pappas and Sarah R. Boggs

Sinusitis is a common illness of childhood and adolescence. There are two common etiologies of acute sinusitis—viral and bacterial—with significant acute and chronic morbidity as well as the potential for serious complications. Fungal sinusitis is rare in immunocompetent patients but can also occur. The common cold produces a viral, self-limited *rhinosinusitis* (see Chapter 428). Approximately 6–7% of viral upper respiratory tract infections in children and adolescents are complicated by acute symptomatic bacterial sinusitis. Some children with underlying predisposing conditions (cystic fibrosis, primary ciliary dyskinesia, immunoglobulin deficiencies) have chronic sinus disease that may or may not be infectious.

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 years of age. The sphenoidal sinuses are present by 5 years of age, whereas the frontal sinuses begin development at age 7–8 years 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 and maintained by the mucociliary clearance system.

The bacterial pathogens causing **acute bacterial sinusitis** in children and adolescents include *Streptococcus pneumoniae* (~30%; see Chapter 228), nontypeable *Haemophilus influenzae* (~50%; see Chapter 240), and *Moraxella catarrhalis* (~10%; see Chapter 242). Approximately 50% of *H. influenzae* and 100% of *M. catarrhalis* are β-lactamase positive. As a result of routine use of pneumococcal conjugate vaccine (PCV) 13 in children, nontypeable *H. influenzae* is the most common cause of acute bacterial sinusitis in children; *S. pneumoniae* resistance has also decreased. Similarly, as a result of routine use of the *H. influenzae* type b vaccination in children, almost all *H. influenzae* infections are nontypeable *H. influenzae*. 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 227.1) 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. *Fusobacterium necrophorum* and *Streptococcus anginosus* are emerging pathogens causing sinusitis with high potential for intracranial extension.

EPIDEMIOLOGY

Acute bacterial sinusitis can occur at any age, though it is more common in older children and adolescents as the sinus cavities become pneumatized. Predisposing conditions may include viral upper respiratory tract infections (associated with out-of-home daycare or a school-age sibling), allergic rhinitis, and tobacco smoke exposure. Children with immune deficiencies, particularly of antibody production (immunoglobulin [Ig]G, IgG subclasses, IgA; see Chapter 166), cystic fibrosis (see Chapter 454), ciliary dysfunction (see Chapter 455), 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 a duration of <30 days, subacute by a duration of 1–3 months, and chronic by a duration of longer than 3 months.

PATHOGENESIS

Acute bacterial sinusitis typically follows a viral upper respiratory tract infection (including COVID-19 infection). Initially, the viral infection produces a viral rhinosinusitis; magnetic resonance imaging (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

Table 429.1 Symptoms of Acute Bacterial Sinusitis

MAJOR SYMPTOMS	MINOR SYMPTOMS
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis
Facial congestion or fullness	Dental pain
Facial pain or pressure alone or exacerbated by bending forward	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (for acute sinusitis only)	Fatigue

Modified from Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *CID*. 2012;54:e72–e112, Table 2.

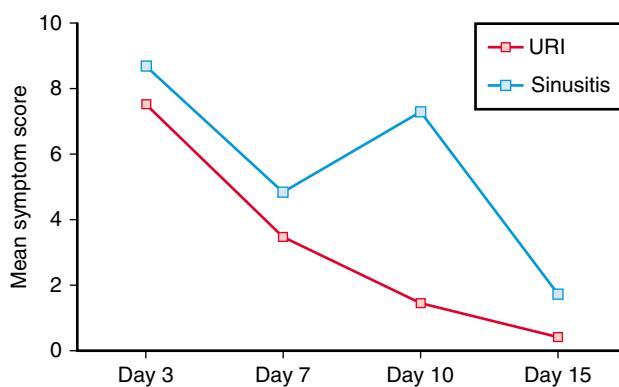


Fig. 429.1 Sinusitis vs URI biphasic symptoms. Mean symptom score by day of illness. (Modified from DeMuri GP, Eickhoff JC, Gern JC, Wald ER. Clinical and virological characteristics of acute sinusitis in children. *Clin Infect Dis*. 2019;69:1764–1770, Fig. 1.)

(unilateral or bilateral), fever, and cough. Less common symptoms include bad breath (halitosis), a decreased sense of smell (hyposmia), and periorbital edema (Table 429.1). Complaints of headache and facial pain are rare in children. Additional symptoms include maxillary tooth discomfort and facial 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.

DIAGNOSIS

The clinical diagnosis of *acute bacterial sinusitis* is based on history, which unfortunately overlaps significantly with that of the common cold. In order to differentiate between the two, current pediatric guidelines define acute bacterial sinusitis as either (1) persistent symptoms of upper respiratory tract infection (rhinitis, common cold), including nasal discharge and/or daytime cough for longer than 10 days without improvement, (2) sudden worsening or new symptoms, known as two-phase illness, or “double sickening,” including nasal discharge, daytime cough, or fever after initial improvement (Fig. 429.1), or (3) severe onset with temperature of at least 39°C (102°F) and purulent nasal discharge for 3–4 consecutive days. Bacteria are recovered from maxillary sinus aspirates in 70% of children with such persistent or severe symptoms. 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 immunocompetent 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 with aspirates. Findings on radiographic studies (sinus plain films, computed tomography [CT]

scans), including opacification, mucosal thickening, or presence of an air–fluid level, are not diagnostic 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 (including COVID-19), 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. In a study using nasal sampling, new viruses were present in 29% of sinusitis episodes in children, suggesting sequential upper respiratory infections (URIs) as the cause of persistent symptoms in many cases. 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. Two randomly controlled trials in children with acute bacterial sinusitis showed improvement after antibiotic therapy, whereas a third 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. Approximately 50% of children with acute bacterial sinusitis recover without antimicrobial treatment. Centers for Disease Control and Prevention (CDC) guidelines offer that either (1) antibiotic treatment is initiated at the time of diagnosis or (2) the clinician/family may choose continued observation for an additional 3 days, with the caveat that antibiotic therapy will be initiated if symptoms worsen or do not improve. Continued observation is generally not recommended for children with persistent symptoms treated with antibiotics in the preceding 30 days or those with underlying conditions.

Due to the high prevalence of antibiotic-resistant *S. pneumoniae* in some communities, amoxicillin-clavulanate is recommended by some authorities as the preferred initial therapy for acute bacterial sinusitis; high-dose amoxicillin alone may also be considered. In a large cohort of pediatric and adolescent patients from a nationwide healthcare utilization database, both antibiotics were equally effective (equivalent treatment failure rates), but those who received amoxicillin-clavulanate had a higher rate of adverse events. Alternative treatments for the penicillin-allergic patient include cefpodoxime, cefdinir, or levofloxacin. *Azithromycin* and *trimethoprim-sulfamethoxazole* are no longer indicated because of a high prevalence of antibiotic resistance. 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. For those with worsening symptoms or failure to improve after 3 days of antibiotic therapy, antibiotic therapy may be changed or the child may be referred to an otolaryngologist for further evaluation (maxillary sinus aspiration for culture and susceptibility testing may be necessary) (Table 429.3). The appropriate duration of therapy for sinusitis has yet to be determined; individualization of therapy is a reasonable approach, with treatment recommended in children for a minimum of 10 days or 7 days after resolution of symptoms. Frontal sinusitis can rapidly progress to serious intracranial complications and may necessitate initiation of parenteral ampicillin-sulbactam, ceftriaxone, or levofloxacin until substantial clinical improvement is achieved (Figs. 429.2 and 429.3). 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 liquefy secretions and act as a mild vasoconstrictor, but the effects have not been systematically evaluated in children.

Table 429.2 Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Children	
INDICATION	TREATMENT
Initial empirical therapy for mild to moderate disease*	Amoxicillin-clavulanate (45 mg amoxicillin/kg/day PO divided bid, max 4 g amoxicillin/day) × 10 days*
Initial therapy for acute worsening ("double sickening") of symptoms OR severe disease†	Amoxicillin-clavulanate (90 mg amoxicillin/kg/day PO divided bid, max 4 g amoxicillin/day) × 10 days
β-Lactam allergy	
Type I hypersensitivity	Levofloxacin (10-20 mg/kg/day PO divided every 12-24 hr, max 500 mg/day) × 10 days
Non-type I hypersensitivity	Cefpodoxime‡ (10 mg/kg/day PO divided bid) × 10 days
Severe infection requiring hospitalization	Ampicillin/sulbactam (200-400 mg ampicillin/kg/day IV divided every 6 hr, max 8 g ampicillin/day) Ceftriaxone (50 mg/kg/day IV divided every 12 hr, max 4 g/day) Levofloxacin (10-20 mg/kg/day IV divided every 12-24 hr, max 500 mg/day)

*Amoxicillin 90 mg/kg/day, divided bid, max 4g/day, can also be considered.

†Acute worsening ("double sickening") OR severe disease: worsening nasal discharge, daytime cough, or fever starting after a period of initial improvement OR severe onset with temperature of at least 39°C (102°F) and purulent nasal discharge for 3-4 consecutive days.

‡Cefdinir (14 mg/kg/day in one or two divided doses, max 600 mg/day) is an alternative that is more palatable in liquid form than cefpodoxime but has less coverage of bacterial sinusitis pathogens.

result from acute bacterial sinusitis and progress rapidly. Organisms causing orbital and/or intracranial complications of bacterial sinusitis in children include members of the *Streptococcus anginosus* group, *S. aureus*, *S. pneumoniae*, methicillin-resistant *S. aureus* (MRSA), and methicillin-sensitive *S. aureus* (MSSA); ~30% of infections were polymicrobial.

Orbital complications, including periorbital cellulitis and more often orbital cellulitis (see Chapter 674), are most often secondary to acute bacterial ethmoiditis. *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. 429.4). In addition to IV antibiotics, orbital cellulitis may require surgical drainage of the ethmoid sinuses or orbit.

Intracranial complications can include epidural abscess, meningitis, cavernous sinus thrombosis, subdural empyema, and brain abscess (see Chapter 644). Children with altered mental status, nuchal rigidity, severe headache, focal neurologic findings, or signs of increased intracranial pressure (headache, vomiting) require immediate CT scan with contrast of the brain, orbits, and sinuses to evaluate for the presence of intracranial complications of acute bacterial sinusitis. Diagnosis of intracranial complications may be challenging, as many patients present with nonspecific symptoms present for the preceding 7-10 days (most commonly headache, fever, congestion, nausea, and vomiting); typically, patients will have been seen by a healthcare provider one or more times before diagnosis. About 50% of patients will present with an abnormal neurologic exam, although only ~30% of patients will present with neurologic symptoms (altered mental status, seizures).

Treatment with broad-spectrum IV antibiotics (usually cefotaxime or ceftriaxone combined with vancomycin and metronidazole) should be initiated immediately, pending culture and susceptibility results. Abscesses can require surgical drainage; endoscopic sinus surgery (ESS) without powered instruments and proper personal protective equipment (PPE) are recommended to minimize risks of aerosolization. Other complications include osteomyelitis of the frontal bone (**Pott puffy tumor**), which is characterized by edema and swelling of the forehead (see Fig. 429.2), and **mucocles**, 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.

Table 429.3 Indications for Referral to a Specialist

Severe infection (high persistent fever with temperature >39°C [$>102^{\circ}\text{F}$], orbital edema, severe headache, visual disturbance, altered mental status, meningeal signs)
Recalcitrant infection with failure to respond to extended courses of antimicrobial therapy
Immunocompromised host
Multiple medical problems that might compromise response to treatment (e.g., hepatic or renal impairment, hypersensitivity to antimicrobial agents, organ transplant)
Unusual or resistant pathogens
Fungal sinusitis or granulomatous disease
Nosocomial infection
Anatomic defects causing obstruction and requiring surgical intervention
Multiple recurrent episodes of acute bacterial rhinosinusitis (three to four episodes per year) suggesting chronic sinusitis
Chronic rhinosinusitis (with or without polyps or asthma) with recurrent acute bacterial rhinosinusitis exacerbations
Evaluation of immunotherapy for allergic rhinitis

From Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *CID*. 2021;54:e72–e112, Table 14.

COMPLICATIONS

Because of the close proximity of the paranasal sinuses to the brain and eyes, serious orbital and/or **intracranial complications** can

PREVENTION

Prevention is best accomplished by frequent handwashing and avoiding persons with colds. This was confirmed most recently in New Zealand: when strict nonpharmaceutical infection control measures were implemented during the COVID-19 pandemic, infections caused by common cold viruses (influenza, respiratory syncytial virus [RSV], human metapneumovirus, enterovirus, adenovirus, parainfluenza virus, and rhinovirus) were greatly reduced. Once restrictions were eased, only rhinovirus infections quickly increased, whereas the prevalence of other respiratory viral infections remained reduced. This may be because of the fact that most rhinovirus infections are transmitted in the home where public restrictions are not in place. Commercially available alcohol-based hand sanitizers have been shown in vitro to be effective against COVID-19 and the common cold viruses.

Because acute bacterial sinusitis can be a complication of influenza infection, prevention of influenza infection by yearly influenza vaccine will prevent some cases of complicating sinusitis. Chemoprophylaxis against influenza with oseltamivir or zanamivir may be useful for prevention of influenza-associated sinusitis.

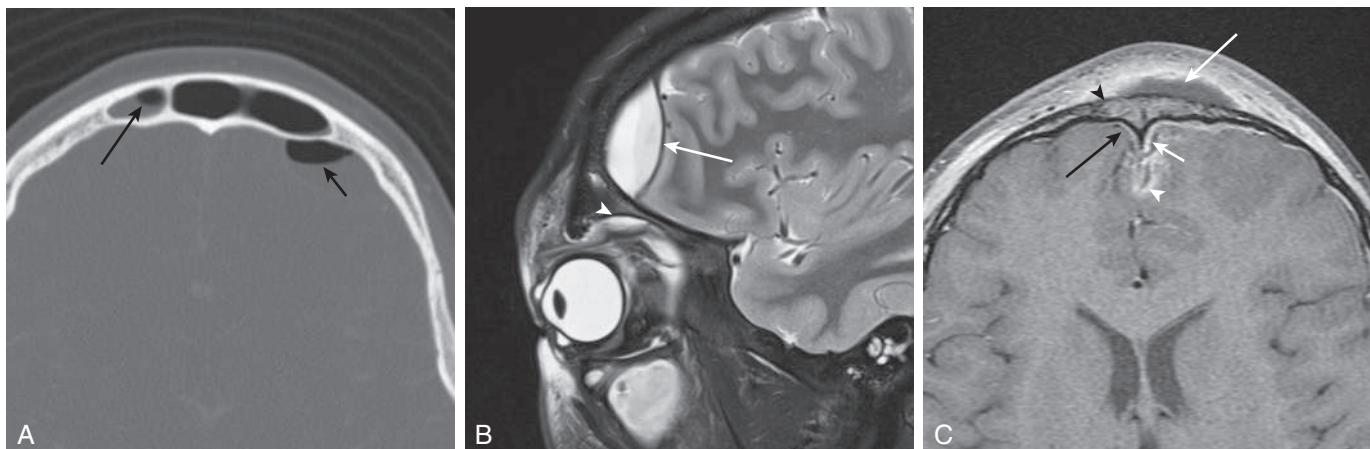


Fig. 429.2 Acute complicated sinusitis. A, Frontal sinusitis and epidural abscess. Axial computed tomography image shows a frontal sinus air-fluid level (long arrow). There is also an intracranial air-fluid level associated with an epidural abscess (short arrow). B, Frontal sinusitis, epidural abscess, and orbital abscess. Sagittal fat-suppressed (FS) T2-weighted magnetic resonance (MR) image demonstrates a biconvex epidural abscess (arrow) containing a sediment level. There is also a small superior extraconal subperiosteal abscess (arrowhead). Periorbital STS is present, and there are secretions within the maxillary antrum. C, Pott puffy tumor, frontal osteomyelitis, and subdural empyema. Axial gadolinium-enhanced FS T1-weighted MR image shows frontal scalp swelling ventral to an elliptical low signal intensity, peripherally enhancing, frontal subperiosteal abscess (long white arrow). There is enhancement of the subjacent frontal bone, consistent with osteomyelitis (black arrowhead). There is also dural enhancement (black arrow) and a small left frontal interhemispheric subdural empyema (short white arrow) with subtle enhancement of the adjacent frontal leptomeninges and cortex caused by meningitis and cerebritis (white arrowhead). (From Walters MM, Robertson RL, eds. *Pediatric Radiology: The Requisites*, 4th ed. Philadelphia: Elsevier; 2017: Fig. 10.40.)



Fig. 429.3 Axial plane contrast-enhanced CT scan of an 11-yr-old obtunded female 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*. 2004;15:37–41.)

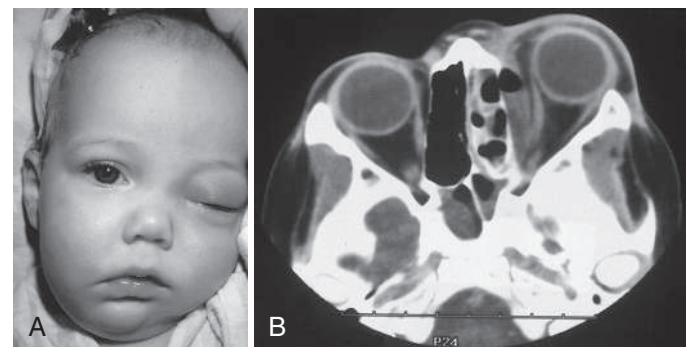


Fig. 429.4 Orbital complications of acute sinusitis. A, An 11-mo-old infant with a swollen left eye and limited ocular movement. B, Axial CT shows opacification of sinuses and an inflammatory mass with an air-fluid level displacing the medial rectus laterally. (From Cooper ML, Slovis T. *The sinuses*. In Slovis T, ed. *Caffey's Pediatric Diagnostic Imaging*, 11th ed. Philadelphia: Mosby; 2008: Fig. 43-7, p. 573.)

Chapter 430

Acute Pharyngitis

Joseph Gigante

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 periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome, Kawasaki disease, multisystem inflammatory syndrome in children (MIS-C), inflammatory bowel disease (IBD), Stevens-Johnson syndrome, and systemic lupus erythematosus (SLE). 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 229) pharyngitis and treating them with antibiotics forms the core of the management paradigm.

INFECTIOUS ETIOLOGIES

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, parainfluenza, adenoviruses, coronaviruses, enteroviruses, rhinoviruses, respiratory syncytial virus (RSV), cytomegalovirus, Epstein-Barr virus (EBV), herpes simplex virus (HSV), and human metapneumovirus (HMPV) (Table 430.1). 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 (Table 430.2). Sore throat is also seen in COVID-19 infection and MIS-C; it is rare to be the only symptom and is part of the multisystem involvement in both disorders.

Table 430.1 Infectious Agents that Cause Pharyngitis

VIRUSES	BACTERIA
Adenovirus	<i>Streptococcus pyogenes</i> (group A streptococcus)
Coronavirus including COVID-19	<i>Arcanobacterium haemolyticum</i>
Cytomegalovirus	<i>Fusobacterium necrophorum</i>
Epstein-Barr virus	<i>Corynebacterium diphtheriae</i>
Enteroviruses	<i>Neisseria gonorrhoeae</i>
Herpes simplex virus (1 and 2)	Group C streptococci
Human immunodeficiency virus	Group G streptococci
Human metapneumovirus	<i>Francisella tularensis</i>
Influenza viruses (A and B)	<i>Yersinia pestis</i>
Measles virus	<i>Chlamydophila pneumoniae</i>
Parainfluenza viruses	<i>Chlamydia trachomatis</i>
Respiratory syncytial virus	<i>Mycoplasma pneumoniae</i>
Rhinoviruses	Mixed anaerobes (Vincent angina)

Gingivostomatitis and ulcerating vesicles throughout the anterior pharynx and on the lips and perioral skin are seen in primary oral HSV 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, 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, lymphadenopathy, or hepatomegaly may be the clue to EBV infectious mononucleosis in an adolescent with exudative tonsillitis. Primary infection with HIV can manifest as **acute retroviral syndrome**, with nonexudative pharyngitis, fever, arthralgia, myalgia, adenopathy, and often a maculopapular rash.

Bacteria Other than Group A Streptococcus

In addition to GAS, bacteria that cause pharyngitis include group C and group G streptococcus, *Arcanobacterium haemolyticum*, *Francisella tularensis*, *Neisseria gonorrhoeae*, *Mycoplasma pneumoniae*, *Chlamydophila* (formerly *Chlamydia*) *pneumoniae*, *Chlamydia trachomatis*, *Fusobacterium necrophorum*, and *Corynebacterium diphtheriae*. *Haemophilus influenzae* and *Streptococcus pneumoniae* may be cultured from the throats of children with pharyngitis, but their role in causing pharyngitis has not been established.

Group C and group G streptococcus and *A. haemolyticum* pharyngitis have been diagnosed most commonly in adolescents and adults.

Table 430.2 Epidemiologic and Clinical Features Suggestive of Group A Streptococcal and Viral Pharyngitis

FEATURE, BY SUSPECTED ETIOLOGIC AGENT

Group A Streptococcal

- Sudden onset of sore throat
- Age 5–15 yr
- Fever
- Headache
- Nausea, vomiting, abdominal pain
- Tonsillopharyngeal inflammation
- Patchy tonsillopharyngeal exudates
- Palatal petechiae
- Anterior cervical adenitis (tender nodes)
- Winter and early spring presentation
- History of exposure to strep pharyngitis
- Scarlatiniform rash
- No cough or coryza

Viral

- Conjunctivitis
- Coryza
- Cough
- Diarrhea
- Hoarseness
- Discrete ulcerative stomatitis
- Viral exanthema
- As part of the spectrum of COVID-19 and MIS-C

From Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55(10):e86–e102, Table 4.

They resemble group A β -hemolytic streptococcus (GABHS) pharyngitis. A scarlet fever-like rash may be present with *A. haemolyticum* infections.

F. necrophorum is an important etiology of pharyngitis in older adolescents and adults (15–30 years old). Prevalence in studies has varied from 10% to 48% of patients with non-GABHS pharyngitis, but large surveillance studies have not been performed. *F. necrophorum* was detected by polymerase chain reaction (PCR) in 20.5% of patients with pharyngitis in a study based in a university health clinic and in 9.4% of an asymptomatic convenience sample; some patients had more than one bacterial species detected by PCR. Pharyngitis patients with *F. necrophorum* had signs and symptoms similar to GAS pharyngitis: ~30% had fever, ~30% had tonsillar exudates, ~65% had anterior cervical adenopathy, and most did not have cough. This organism is difficult to culture from the throat, and diagnostic testing with PCR is not generally available. *F. necrophorum* pharyngitis is associated with the development of **Lemierre syndrome** (see Chapter 432): 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 shock 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 ulcerative or exudative 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 because of extensive immunization with diphtheria 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.

Group A Streptococcus

Streptococcal pharyngitis is relatively uncommon before 2–3 years of age, is quite common among children 5–15 years 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 (see Table 430.2). The pharynx is red, and 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 (see Table 430.2).

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 less intensely red (more pale), giving the appearance of circumoral 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 lines or sign). Pastia lines are sometimes petechial or slightly hemorrhagic. Capillary fragility can cause petechiae distal to a tourniquet or constriction from clothing, a positive tourniquet test or Rumpel-Leeds phenomenon. Erythema fades in a few days, and when the rash resolves, it typically peels like a mild sunburn. Sometimes there is sheetlike desquamation around the free margins of the fingernails. 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 and determines the M type (or *emm* type). Molecular methods have identified more than 240 *emm* genes (*emm* types, M types). The M protein is immunogenic and protects against reinfection with the homologous M type; an individual can experience multiple episodes of GAS pharyngitis in a lifetime because natural immunity is M type-specific and does not prevent infection with a new M type. 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 clinical judgment often overestimate the likelihood of a streptococcal etiology. Various clinical scoring systems have been described to assist in identifying patients who are likely to have GAS pharyngitis. Criteria developed for adults by Centor and modified for children by McIsaac give one point for each of the following criteria: history of temperature $>38^{\circ}\text{C}$ (100.4°F), absence of cough, tender anterior cervical adenopathy, tonsillar swelling or exudates, and age 3–14 years. It subtracts a point for age ≥ 45 years. At best, a McIsaac score ≥ 4 is associated with a positive laboratory test for GAS in less than 70% of children with pharyngitis (Table 430.3), so it, too, overestimates the likelihood of GAS. Consequently, laboratory testing is essential for an accurate diagnosis. Clinical findings and/or scoring systems can best be used to assist the clinician in identifying patients in need of testing. Evaluating patients indiscriminately can lead to overdiagnosis and overtreatment. Streptococcal antibody tests are not useful in assessing patients with acute pharyngitis.

Throat culture, rapid antigen-detection tests (RADTs), or PCR tests are the diagnostic tests for GAS most available in routine clinical care. Throat culture plated on blood agar remains the gold standard for diagnosing streptococcal pharyngitis. There are both false-negative cultures as a consequence of sampling errors or prior antibiotic treatment and false-positive cultures as a consequence of misidentification of other bacteria as GAS. Streptococcal RADTs detect the group A carbohydrate of GAS. They are used by the vast majority of office-based pediatricians. All RADTs have very high specificity, generally $\geq 95\%$, so when a RADT is positive, it is assumed to be accurate and throat culture is unnecessary. Because RADTs are generally much less sensitive than culture, confirming a negative rapid test with a throat culture is recommended. RADTs and throat culture exhibit spectrum bias: they are more sensitive when the pretest probability of GAS is high (signs and symptoms are typical of GAS infection, higher McIsaac scores) and less sensitive when the pretest probability is low. Avoidance of testing when patients have signs and symptoms more suggestive of a viral infection is recommended by expert guidelines.

Table 430.3 Positive Predictive Value of McIsaac Score in Children in Clinical Studies*

SCORE	McISAAC, 2004 (n = 454) (%)	EDMONSON, 2005 (n = 1184) (%)	TANZ, 2009 (n = 1848) (%)	FINE, 2012 (n = 64,789) (%)
0	—	—	7	17
1	—	0.5	19	23
2	20.5	8.9	20	34
3	27.5	42.4	29	50
≥4	67.8	48.2	49	68
GAS prevalence	34	38	30	37

*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.

Many laboratories have replaced throat culture with one of the highly sensitive and specific **GAS molecular tests**. A variety of methods are available to amplify the DNA of a specific GAS gene from a throat swab in less than 1 hour. In studies both sensitivity and specificity are reported to be ≥98% when compared with standard throat culture. PCR usually matches the molecular test when used to adjudicate discrepancies between the culture and molecular test results. Some of these nucleic acid amplification tests are approved by the FDA for use in physician office laboratories and can be used as the initial test for GAS or as a confirmatory test when the RADT is negative. Unlike throat culture and RADTs, molecular tests may not exhibit spectrum bias—that is, although test sensitivity is extremely high, it is independent of the pretest probability that GAS is the cause of illness (using signs and symptoms, McIsaac score), thus increasing the potential to identify a chronic GAS carrier who actually has an intercurrent illness not caused by GAS (discussed later). However, the ability of these stand-alone tests to deliver a definitive result in less than 1 hour makes them attractive (there is one test that takes 15 minutes)—the potential to swab symptomatic children, have them wait or send them home, and electronically prescribe an antibiotic when the test is positive can speed initiation of therapy and subsequent return to school and activities. Concerns about molecular tests include the following: (1) they are so sensitive they may cause unnecessary treatment of more patients who are carriers than would ordinarily occur with RADT and/or culture; (2) unless rigorous technique is followed, they may be prone to contamination with exogenous GAS DNA from other swabs, a particular concern in physician offices when performed by staff who are not trained laboratory technologists; and (3) they are much more expensive than throat culture.

Testing for bacteria other than GAS is performed infrequently and should be reserved for patients with persistent symptoms and symptoms suggestive of a specific non-GAS bacterial pharyngitis—for example, when there is concern for gonococcal infection or sexual abuse. Special culture media and a prolonged incubation are required to detect *A. haemolyticum*. A complete blood cell count showing many atypical lymphocytes and a positive mononucleosis slide agglutination test can help confirm a clinical suspicion of EBV infectious mononucleosis. Viral cultures are often unavailable and are generally too expensive and slow to be clinically useful. PCR is more rapid, and multiplex PCR (respiratory viral panel) testing for respiratory pathogens can identify a variety of viral and bacterial agents within a few hours. This may be useful in determining the isolation needs of hospitalized patients, assisting in patient prognosis, and epidemiology, but in the absence of specific treatment for most viral infections, such testing is usually not necessary or useful. In fact, interpreting such tests can be difficult unless the patient has signs or symptoms characteristic of a specific pathogen.

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 (acetaminophen 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 appropriate to use them. Systemic corticosteroids are sometimes used in children who have evidence of upper airway compromise caused by mononucleosis. Although corticosteroids are used 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 cases of 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 uneventfully within a few days, but early antibiotic therapy hastens clinical recovery by 12–24 hours and also reduces suppurative complications of GAS pharyngitis such as peritonsillar abscess and cervical adenitis. *The primary benefit and intent of antibiotic treatment is the prevention of acute rheumatic fever (ARF);* it is highly effective when started within 10 days of onset of illness. Antibiotic therapy does not prevent acute poststreptococcal glomerulonephritis (APSGN). Antibiotic treatment should not be delayed for children with symptomatic pharyngitis and a positive test for GAS. Presumptive antibiotic treatment can be started when there is a clinical diagnosis of scarlet fever, a symptomatic child has a household contact with documented streptococcal pharyngitis, or there is a history of ARF in the patient or a family member, but a diagnostic test should be performed to confirm the presence of GAS, and antibiotics should be discontinued if GAS is not identified.

A variety of antimicrobial agents are effective for GAS pharyngitis (**Table 430.4**). Group A streptococci are universally susceptible to penicillin and all other β-lactam antibiotics. Penicillin is inexpensive, has a narrow spectrum of activity, and has few adverse effects. Amoxicillin is often preferred for children because of its taste, availability as chewable tablets and liquid, and the 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 the penicillins 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. Frequently, 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

Table 430.4 Recommended Treatment for Acute Streptococcal Pharyngitis

MOST PATIENTS

	WEIGHT <27 KG	WEIGHT ≥27 KG	ROUTE	DURATION
Amoxicillin	50mg/kg once daily (maximum 1,000 mg)		Oral	10 days
Penicillin V	250mg bid	500mg bid	Oral	10 days
Benzathine penicillin G	600,000 units	1.2 million units	IM	Once
Benzathine penicillin G + procaine penicillin G	900,000 units + 300,000 units	900,000 units + 300,000 units	IM	Once

PENICILLIN-ALLERGIC PATIENTS

	ORAL DOSE	FREQUENCY	DURATION
Cephalosporins*	Varies with agent chosen		10 days
Erythromycins			
Ethylsuccinate	40mg/kg/day up to 1,000mg/day	bid	10 days
Estolate	20-40mg/kg/day up to 1,000mg/day	bid	10 days
Clarithromycin	15mg/kg/day up to 500mg/day	bid	10 days
Azithromycin†	12mg/kg day 1; 6mg/kg days 2-5	qd	5 days
Clindamycin	20mg/kg/day up to 1.8g/day	tid	10 days

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

†Maximum dose is 500 mg the first day and 250 mg subsequent days.

countries. Approximately 5% 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. Rates are much higher in many European and Asian 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. The use of macrolides and related 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

Streptococcal carriers are patients who continue to harbor GAS in the pharynx despite appropriate antibiotic therapy or when they are well. They have little or no evidence of an inflammatory response to the organism. The pathogenesis of chronic carriage is not known; it is assuredly not related to penicillin resistance or nonadherence to therapy, and there is little direct evidence to support the concept of co-pathogenicity (presence of β -lactamase-producing organisms in the pharynx). Carriage generally poses little risk to patients and their contacts, but it can confound testing in subsequent episodes of sore throat. A child who is chronically colonized with GAS (streptococcal carrier) can have a positive test for GAS if it is obtained when the child is evaluated for pharyngitis that is actually caused by a viral infection. 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 clinical pharyngitis should be undertaken without regard for chronic carriage, using clinical criteria to determine the need for testing, treating test-positive patients in routine fashion, and avoiding antibiotics in patients who have negative tests. This approach often requires considerable effort to reassure the patient and family that chronic carriage is not a significant health risk. 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 three doses; adult dose 150-450 mg tid). Amoxicillin-clavulanate (40 mg amoxicillin/kg/day up to 2,000 mg amoxicillin/day divided tid for 10 days) and 4 days of oral rifampin (20 mg/kg/day up to 600 mg divided in two doses) plus either intramuscular benzathine penicillin given once or oral penicillin given for 10 days have also been used (rifampin is started on the first day of penicillin therapy).

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.

Tonsillectomy may lower the incidence of pharyngitis for 1-2 years among children with frequent episodes of documented pharyngitis (\geq 7 episodes in the previous year or \geq 5 in each of the preceding 2 years, or \geq 3 in each of the previous 3 years). However, the frequency of pharyngitis (GAS and non-GAS) generally declines over time without tonsillectomy. By 2 years 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. *Undocumented history of recurrent pharyngitis is an inadequate basis for recommending tonsillectomy.*

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 week) 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 SLE or IBD. 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 pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS, sometimes referred to as CANS [childhood acute neuropsychiatric symptoms] or PANS [pediatric acute-onset neuropsychiatric syndrome], recognizing that many infections other than GAS may predispose to these syndromes).

PREVENTION

Vaccines intended to prevent infection with various viruses (e.g., RSV) and GAS are being developed. A recombinant multivalent GAS M-type vaccine uses the terminal portions of various M proteins to take advantage of their immunogenicity. Other GAS vaccines are based on more conserved 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. A recent comprehensive study of the immune response to childhood GAS pharyngeal acquisition raises questions about how to best design effective vaccines. This is complicated by the variety of clinical scenarios and clinical syndromes associated with GAS and the need to determine the intended clinical benefit(s) of vaccination. Antimicrobial prophylaxis with daily oral penicillin prevents recurrent GAS infections but is recommended only to prevent recurrences of ARF.

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Chapter 431

Tonsils and Adenoids

Karen B. Zur

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). 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 years of age, with a decrease after puberty. Adenotonsillar hypertrophy is greatest between ages 3 and 6 years; in most children tonsils begin to involute after age 8 years. 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 430). Group A β -hemolytic streptococcus (GABHS) is the most common cause of bacterial infection in the pharynx (see Chapter 229).

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 tonsilloliths. Biofilms appear to play a role in chronic inflammation of the tonsils.

Upper Airway Obstruction

Enlargement of the tonsils and/or adenoids is 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 31). Sleep-disordered breathing secondary to adenotonsillar hypertrophy is a cause of growth failure. Solid dysphagia can also be seen in this group of patients, with symptoms such as prolonged chewing, pocketing of solids in the mouth, choking or gagging when swallowing solids, and weight loss.

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. 431.1; see Chapter 229).

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, often containing copious debris within the crypts. The offending organism is not usually GABHS.

Airway Obstruction

The diagnosis of airway obstruction (see Chapter 31) 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, hyposmia,



Fig. 431.1 Pharyngotonsillitis. This common condition has a number of causative pathogens and a wide spectrum of severity. **A**, The diffuse tonsilar and pharyngeal erythema seen here is a nonspecific finding that can be produced by a variety of pathogens. **B**, This intense erythema, seen in association with acute tonsillar enlargement and palatal petechiae, is highly suggestive of group A β -streptococcal infection, though other pathogens can produce these findings. **C**, This picture of exudative tonsillitis is most commonly seen with either group A streptococcal or Epstein-Barr virus infection. (**B** courtesy Michael Sherlock, MD, Lutherville, MD. From Yellon RF, McBride TP, Davis HW. *Otolaryngology*. In Zitelli BJ, Davis HW, eds. *Atlas of Pediatric Physical Diagnosis*, 4th ed. Philadelphia: Mosby; 2002:852.)

decreased appetite, poor school performance, hyperactivity, and, rarely, symptoms of right-sided heart failure. Nighttime symptoms consist of loud snoring, choking, gasping, frank apnea, restless sleep, abnormal sleep positions, sleep walking, 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.

These daytime and nocturnal comorbidities should be explored in patients with enlarged tonsils and/or adenoids. Sleep studies (polysomnograms, PSG) are not routinely recommended unless significant co-morbidities exist.

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 tonsillar malignancy should also be entertained if the tonsil appears grossly abnormal. Among 54,901 patients undergoing tonsillectomy, 54 malignancies were identified (0.08% prevalence); all but 6 malignancies had been suspected based on suspicious anatomic features preoperatively.

TREATMENT

Medical Management

The treatment of acute pharyngotonsillitis is discussed in Chapter 430 and antibiotic treatment of GABHS in Chapters 229 and 430. 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. A tonsillolith or debris may be expressed manually with either a cotton-tipped applicator, gargling after meals, or the use of a water jet.

Tonsillectomy

The American Academy of Otolaryngology (AAO)-Head and Neck Surgery Taskforce on Clinical Practice Guidelines: *Tonsillectomy in Children* most recently issued evidence-based guidelines in 2019 (Table 431.1, Fig. 431.2).

Tonsillectomy alone is most often performed for recurrent or chronic pharyngotonsillitis, and in young children is often accompanied by an adenoidectomy (see next section). 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 severely affected patients. In resistant cases of cryptic tonsillitis, tonsillectomy may be curative. The 2019 guidelines recommend watchful waiting for recurrent throat infections

Table 431.1		Paradise Criteria for Tonsillectomy
CRITERION	DEFINITION	
Minimum frequency of sore throat episodes	At least seven episodes in the previous year OR at least five episodes in each of the previous 2 years OR at least three episodes in each of the previous 3 years	
Clinical features	Sore throat <i>plus</i> at least one of the following features qualifies as a counting episode: <ul style="list-style-type: none"> • Temperature of greater than 38.3°C (101°F) OR • Cervical adenopathy (tender lymph nodes or lymph node size >2 cm) OR • Tonsillar exudate OR • Culture positive for group A β-hemolytic streptococcus 	
Treatment	Antibiotics had been administered in the conventional dosage for proven or suspected streptococcal episodes	
Documentation	Each episode of throat infection and its qualifying features substantiated by contemporaneous notation in a medical record OR If the episodes are <i>not fully documented</i> in the patient record, subsequent observation by a physician of two episodes of throat infection with patterns of frequency and clinical features consistent with the initial history*	

*Allows for tonsillectomy recommendation in patients who meet all but the documentation criterion. A 12-mo observation period is usually recommended before consideration of tonsillectomy because of the tendency to improve with time. Adapted from Mitchell RB, Archer SM, Ishman SL, et al. Clinical practice guideline: tonsillectomy in children (update). *Otolaryngol Head Neck Surg*. 2019;160(1S):S1–S42, Table 5.

if there have been <7 episodes in the past year, <5 episodes/yr in the past 2 years, or <3 episodes/yr in the past 3 years (see Table 431.1 and Fig. 431.2).

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 infectious symptoms 2 years after surgery unless other factors or comorbidities exist. However, the 2019 Clinical Practice Guidelines did recommend assessing for additional modifying factors that may favor the need for a tonsillectomy,

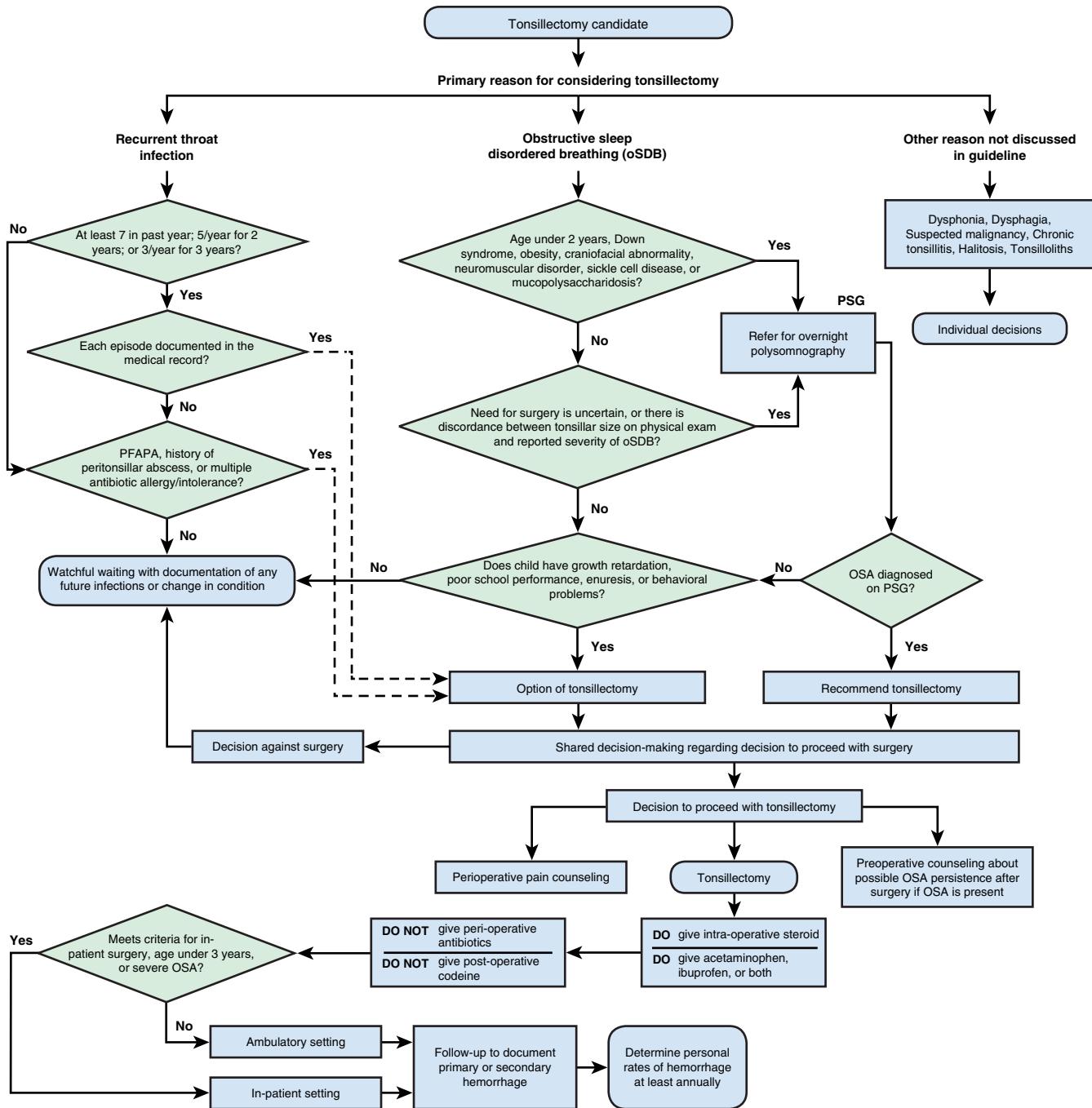


Fig. 431.2 Tonsillectomy in children: clinical practice algorithm. OSA, Obstructive sleep apnea; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis; PSG, polysomnography. (Modified from Mitchell RB, Archer SM, Ishman SL, et al. Clinical practice guideline: tonsillectomy in children, update. *Otolaryngol Head Neck Surg*. 2019;160:S1–S42, Fig. 2.)

including intolerance or allergies to antibiotics, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis), or a history of more than one peritonsillar abscess (PTA).

Adenoidectomy

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 otorrea. 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 a tonsillectomy and adenoidectomy (T&A) for recurrent infections 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-disordered

Table 431.2	Role of PSG in Assessing High-Risk Populations Before Tonsillectomy for oSDB
ROLE OF PSG	RATIONALE
Avoid unnecessary or ineffective surgery in children with primarily nonobstructive events	Identify primarily nonobstructive events or central apnea that may not have been suspected before the study and may not benefit from surgery
Confirm the presence of obstructive events that would benefit from surgery	The increased morbidity of surgery in high-risk children requires diagnostic certainty before proceeding
Define the severity of oSDB to assist in preoperative planning	Children with severe OSA may require preoperative cardiac assessment, pulmonary consultation, anesthesia evaluation, or postoperative inpatient monitoring in an intensive care setting
Provide a baseline PSG for comparison after surgery	Persistent OSA despite surgery is more common in high-risk patients than in otherwise healthy children
Document the baseline severity of oSDB	High-risk patients are more prone to complications of surgery or anesthesia

OSA, Obstructive sleep apnea; oSDB, obstructive sleep-disordered breathing; PSG, polysomnography.

From Mitchell RB, Archer SM, Ishman SL, et al. Clinical practice guideline: tonsillectomy in children (update). *Otolaryngol Head Neck Surg*. 2019;160(1S):S1–S42, Table 6.

breathing experience significant growth acceleration after a T&A. Most children do not require a sleep study before surgery; however, in a high-risk population, polysomnography may help in the decision for or against surgery (Table 431.2). High risk factors include age under 2 years, Down syndrome, obesity, craniofacial abnormality, neuromuscular disorder, sickle cell disease, and mucopolysaccharidosis.

COMPLICATIONS

Poststreptococcal Glomerulonephritis and Acute Rheumatic Fever

The two major complications of untreated GABHS infection are poststreptococcal glomerulonephritis and acute rheumatic fever (see Chapters 559.4 and 229).

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 432). 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 medially with 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 432).

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

Table 431.3	Risks of Tonsillectomy or Adenoidectomy or Both
Cost	
Risk of anesthetic events	<ul style="list-style-type: none"> • Malignant hyperthermia • Cardiac arrhythmia • Vocal cord trauma • Aspiration with resulting bronchopulmonary obstruction or infection • Postoperative nausea and vomiting (PONV)
Risk of miscellaneous surgical or postoperative complications	<ul style="list-style-type: none"> • Pain • Dysphagia • Hemorrhage • Airway obstruction from edema of tongue, palate, or nasopharynx, or retropharyngeal hematoma • Prolonged muscular paralysis • Dehydration • Palatopharyngeal insufficiency • Facial edema • Trauma: dental, larynx, vessels, pharyngeal wall, soft palate • Laryngospasm • Mediastinitis • Cardiac arrest

Modified from Bluestone CD, ed. *Pediatric Otolaryngology*, 4th ed. Philadelphia: WB Saunders; 2003:1213.

drainage if an abscess is demonstrated on CT (see Chapter 432). Septic thrombophlebitis of the jugular vein, **Lemierre syndrome**, manifests with fever, toxicity, neck pain and stiffness, and respiratory distress caused by 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 301) 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 anticoagulation.

Recurrent or Chronic Pharyngotonsillitis

See Chapter 430.

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 431.3). The mortality is low (~0.007%); most often associated with other complex medical conditions. Dehydration caused by odynophagia (painful swallowing) is not uncommon in the first postoperative week. The child is encouraged to drink liquids; however, early resumption of a solid diet is also recommended to help with the pain and return of oral function.

Postoperative pain needs to be managed, and opioid-free tonsillectomies are now recommended. Clinicians are encouraged to counsel the caregivers about the importance of hydration and managing postoperative pain with nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen and to reinforce this information on the day of surgery. The child is encouraged to hydrate, chew, and rest. Codeine is associated with excessive sedation and fatalities and is *not* recommended.

Bleeding can occur in the immediate postoperative period or be delayed after separation of the eschar. The risk of bleeding is variable among institutions, ranging in the literature from 0.1 to 7.5% and averaging around 4.2% in the first 10 days after surgery. Although recurrent bleeding is unlikely, a bleeding diathesis should be ruled out if it occurs.

The updated 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, and it could be used as a supplement to the pain management regimen.

Routine use of antibiotics in the postoperative period is ineffective, and thus the AAO Clinical Practice Guidelines advise against its use.

Swelling of the tongue and uvula can lead to acute airway obstruction and globus sensation in the first few hours after surgery. Children with underlying hypotonia (trisomy 21) or craniofacial anomalies are at greater risk for suffering this complication.

Rare complications include anesthesia-related issues (malignant hyperthermia, arrhythmias, intubation trauma, aspiration), velopharyngeal insufficiency, nasopharyngeal or oropharyngeal stenosis, torticollis, and, very rarely, death from uncontrolled bleeds.

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Chapter 432

Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

Diane E. Pappas and Sarah R. Boggs

The *retropharyngeal* and the *lateral pharyngeal lymph nodes* that drain the mucosal surfaces of the upper airway and digestive tracts are located in the neck within the *retropharyngeal space* (located between the pharynx and the cervical vertebrae and extending down into the superior mediastinum) and the *lateral pharyngeal space* (bounded by the pharynx medially, the carotid sheath posteriorly, and the muscles of the styloid process laterally). The lymph nodes in these deep neck spaces communicate with each other, allowing bacteria from either cellulitis or node abscess to spread to other nodes. Infection of the nodes usually occurs as a result of extension from a localized infection 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 three 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 years of age; as the retropharyngeal nodes involute after 5

years of age, infection in older children and adults is much less common. In the United States, abscess formation occurs most commonly in winter and early spring. Males are affected more often than females, 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. 432.1 and 432.2). Deep neck infections can be accurately identified and localized with CT scans, 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 lymph node 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 229), oropharyngeal anaerobic bacteria (see Chapter 259), and *Staphylococcus aureus* (see Chapter 227.1). In children younger than age 2 years, there has been an increase in the incidence of retropharyngeal abscess, particularly with *S. aureus*, including methicillin-resistant strains. Other pathogens can include *Haemophilus influenzae*, *Klebsiella*, and *Mycobacterium avium-intracellulare*. When a retropharyngeal abscess is associated with cervical osteomyelitis, it may be secondary to retropharyngeal extension to the vertebral body (often polymicrobial) or a primary osteomyelitis with extension to the retropharyngeal space. In endemic areas and among patients at risk for tuberculosis, Pott disease should be considered (Fig. 432.3).

Treatment options include intravenous antibiotics with or without surgical drainage. Empiric antibiotic coverage should be guided by local susceptibility patterns for *S. aureus*. Initial therapy should include either ampicillin-sulbactam (50 mg ampicillin/kg every 6 hours, max 2000 mg ampicillin/dose) or clindamycin (15 mg/kg every 8 hours, max 600 mg/dose). For patients who are ill-appearing at presentation or who do not improve after 24-48 hours of antibiotic therapy, consideration should be given to the addition of either vancomycin or linezolid for coverage of methicillin-resistant *S. aureus* (MRSA). When narrowing antibiotic selection based on culture results, it is important to remember that these infections are typically polymicrobial and some pathogens, particularly oral anaerobes, may not be easily cultured.

Studies show that >50% of children with retropharyngeal or lateral pharyngeal abscess as identified by CT can be successfully treated without surgical drainage; the older the child, the more likely it is that antimicrobial treatment alone will be successful. Drainage is necessary in the patient with respiratory distress or failure to improve with intravenous antibiotic treatment. The typical treatment course is intravenous antibiotic therapy for several days until the patient has begun to improve, followed by a course of oral antibiotics for an additional 14 days. Amoxicillin-clavulanate (90 mg amoxicillin/kg/day, divided every 12 hours, max 2000 mg amoxicillin/dose) or clindamycin (13 mg/kg every 8 hours, max 450 mg/dose) are recommended oral regimens. Complications of retropharyngeal or lateral pharyngeal abscess include significant upper airway obstruction, rupture leading to

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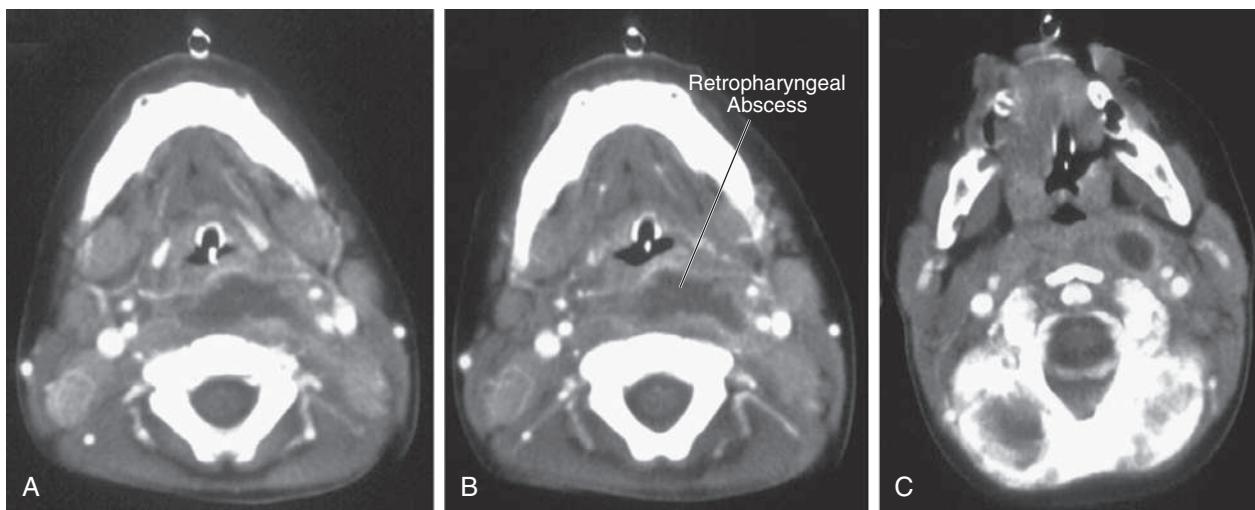


Fig. 432.1 CT of retropharyngeal abscess. A, CT image at level of epiglottis. B, Sequential CT slice exhibiting ring-enhancing lesion. C, Further sequential CT slice demonstrating inferior extent of lesion. (From Philpott CM, Selvadurai D, Banerjee AR. Paediatric retropharyngeal abscess. *J Laryngol Otol.* 2004;118:925.)

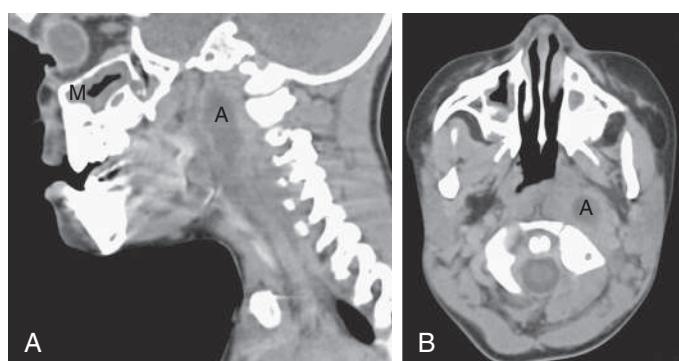


Fig. 432.2 CT of parapharyngeal abscess in a 3-yr-old child. A, Sagittal section demonstrating parapharyngeal abscess (A) and mucosal swelling (M) in the maxillary sinus. B, Coronal section of parapharyngeal abscess (A).

aspiration pneumonia, and extension to the mediastinum with resultant mediastinitis. 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 and embolic abscesses in the lungs (Fig. 432.4). The causative pathogen is *Fusobacterium necrophorum*, an anaerobic bacterial constituent of the oropharyngeal flora. The typical presentation is that of a previously healthy adolescent or young adult with a history of recent pharyngitis who becomes acutely ill with fever and septic pulmonary emboli producing hypoxia, tachypnea, and respiratory distress. Other upper respiratory infections (parotitis, otitis media, mastoiditis, sinusitis, and dental infections) are much less likely to precipitate Lemierre disease. There is a known association with recent Epstein-Barr infection.

Chest x-ray or CT demonstrates multiple cavitary nodules, often bilateral and often accompanied by pleural effusion. Blood culture may be positive. Treatment involves prolonged intravenous antibiotic therapy with either piperacillin-tazobactam, imipenem or meropenem, or ceftriaxone plus metronidazole; vancomycin should be added in areas with a high prevalence of MRSA. Surgical drainage of extrapulmonary metastatic abscesses may occasionally be necessary (see Chapters 430 and 431).



Fig. 432.3 Pott disease. Cervical spine radiography, lateral view, showed prevertebral soft tissue anterior to the C1-C7 level (white arrow), focal destruction of the C3 vertebra (black arrow), and straightening of the cervical spine. (Modified from Hsu HE, Chen CY. Tuberculous retropharyngeal abscess with Pott disease and tuberculous abscess of the chest wall – a case report. *Medicine.* 2019;98:e16280, Fig. 1A.)

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, muffled or garbled voice, 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, but small studies in adults and children have demonstrated that ultrasound may be used to differentiate

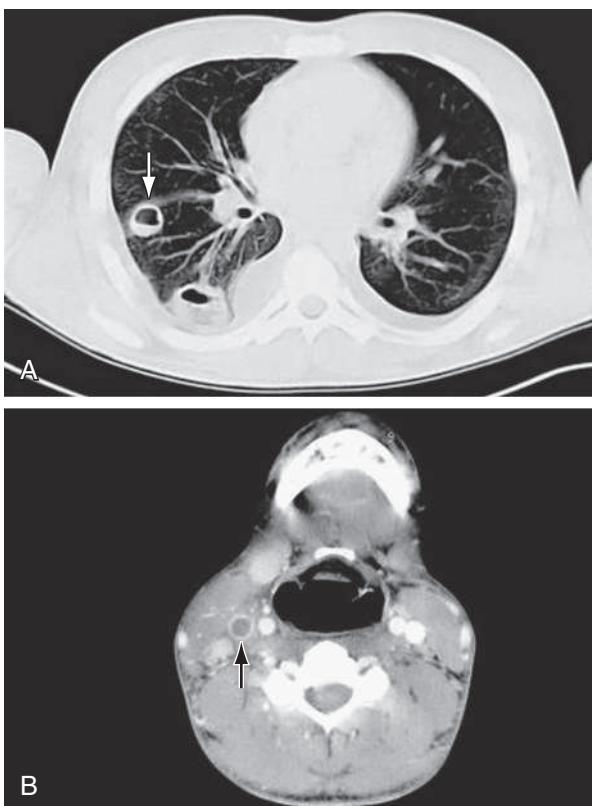


Fig. 432.4 CT of Lemierre disease. A, CT demonstrating the nodular appearance of pulmonary infiltrates (arrow). B, CT of the neck demonstrating thrombosis of the right internal jugular vein (arrow). (From Plymeyer MR, Zoccola DC, Tallarita G. An 18 year old man presenting with sepsis following a recent pharyngeal infection. *Arch Pathol Lab Med*. 2004;128:813. Copyright 2004. College of American Pathologists.)

peritonsillar abscess from peritonsillar cellulitis and avoids radiation exposure, as well as the need for sedation that CT often necessitates in children. Group A streptococci and mixed oropharyngeal anaerobes are the most common pathogens, with more than four bacterial isolates per abscess typically recovered by needle aspiration.

A study in Britain evaluating the impact of outpatient management recommendations (increased outpatient or short-stay management, drainage under local anesthetic, prompt discharge) found that admissions were reduced by over 50% and aspiration under local anesthetic increased with no change in readmission or mortality rates. Similarly, a U.S. study found that initial outpatient management is associated with greater use of antibiotics alone and less frequent use of incision and drainage; the recurrence rate was the same regardless of inpatient or outpatient management. These studies suggest that initial outpatient management of peritonsillar abscess in pediatric patients should be considered, especially for older patients who have mild to moderate symptoms; inpatient therapy is indicated for younger patients and those presenting with more severe illness, including trismus and odynophagia. Either amoxicillin-clavulanate or clindamycin would be an acceptable oral regimen.

Inpatient therapy is indicated for younger patients and for those presenting with more severe illness, including significant trismus and odynophagia. If outpatient management with antibiotics alone is unsuccessful or if inpatient management is indicated initially, treatment consists of surgical drainage or needle aspiration along with intravenous antibiotic therapy. As with retropharyngeal abscesses, empiric antibiotic therapy should include either ampicillin-sulbactam or clindamycin, with the addition of vancomycin in patients who are not improving or in areas with high rates of MRSA.

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 hours of antibiotic therapy and needle aspiration, 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 pneumonitis. There is a 10% recurrence risk for peritonsillar abscess.

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Chapter 433

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

Kristine Knuti Rodrigues and Genie E. Roosevelt

Airway resistance is inversely proportional to the fourth power of the radius (see Chapter 421). Because the lumen of an infant's or child's airway is narrow, minor reductions in cross-sectional area resulting from 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 four 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 years of age.

Inflammation involving the vocal cords and structures inferior to the cords is called **laryngitis**, **laryngotracheitis**, or **laryngotracheobronchitis**, 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 metallic/brassy cough and may be associated with hoarseness, inspiratory stridor, and respiratory distress. **Stridor** is a harsh, high-pitched respiratory sound that 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 421). Croup typically affects the larynx, trachea, and bronchi. When the involvement of the larynx is sufficient to produce symptoms, these symptoms dominate the clinical picture more so than 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 because studies have documented viral etiologies in both acute and recurrent croup.

433.1 Infectious Upper Airway Obstruction

Kristine Knuti Rodrigues and Genie E. Roosevelt

With the exceptions of diphtheria (see Chapter 233), bacterial tracheitis, and epiglottitis, most other acute infections of the upper airway are caused by viruses. The parainfluenza viruses (types 1, 2, and 3; see Chapter 306) account for approximately 75% of cases; other viruses associated with croup include influenza A and B, adenovirus, respiratory syncytial virus, COVID-19, 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 269). Most patients with croup are between the ages of 3 months and 5 years, with the peak in the second year of life. The incidence of croup is higher in males. It occurs most commonly in the late fall and winter but can occur throughout the year. Approximately 15% of patients have a strong family history of croup. Recurrences are frequent from 3 to 6 years of age and decrease with growth of the airway. Recurrent croup is defined as two or more croup-like episodes. Patients with recurrent croup have a higher incidence of asthma, allergies, and gastroesophageal reflux; less than 9% of patients with recurrent croup demonstrate clinically significant findings on bronchoscopy (e.g., subglottic stenosis, reflux changes, bronchomalacia/tracheomalacia).

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 240). Therefore other agents, such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, nontypable *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 years of age, although cases were seen in the first year of life and in patients as old as 7 years of age. Currently, the most common presentation of epiglottitis is an adult with a sore throat, although cases still do occur in underimmunized children or with other less common bacteria; vaccine failures have rarely 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. Other family members might have mild respiratory illnesses with laryngitis. Most young patients with croup progress only as far as stridor and slight dyspnea before they start to recover.

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, infrasternal, and intercostal retractions; and continuous stridor. Croup is a disease of the upper airway, and alveolar gas exchange is usually normal.

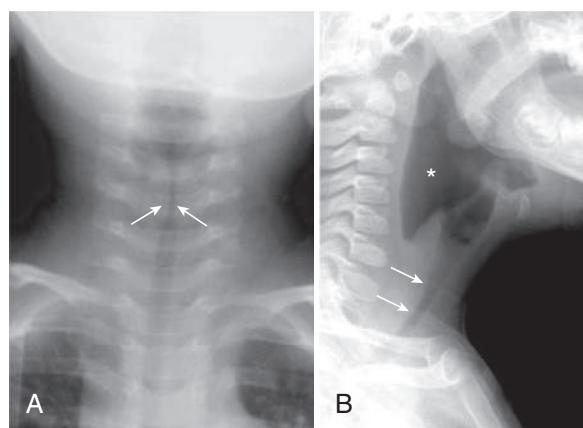


Fig. 433.1 Croup. A, Frontal soft tissue neck radiograph demonstrates a “steeple” appearance of the subglottic trachea (arrows). B, Lateral soft tissue neck radiograph in another patient shows a dilated hypopharynx (asterisk), along with haziness and narrowing of the subglottic region (arrows). (From Laya BF, Lee EY. Upper airway disease. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 51.8, p. 481.)

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. 433.1). 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 first undergo lateral radiographs of the upper airway. Classic radiographs of a child who has epiglottitis show the thumb sign (Fig. 433.2). Proper positioning of the patient for the lateral neck radiograph is crucial 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 intubation equipment should accompany patients with suspected epiglottitis at all times. An older cooperative child might voluntarily open the mouth wide enough for a direct view of the inflamed epiglottis.

Establishing an airway by endotracheal or nasotracheal intubation or, less often, by tracheostomy is indicated in patients with epiglottitis, regardless of the degree of apparent respiratory distress, because as many as 6% of children with epiglottitis without an artificial airway die compared with <1% of those with an artificial airway. No clinical features have been recognized that predict mortality. Pulmonary edema can be associated with acute airway obstruction. The duration of intubation depends on the clinical course of the patient and the duration of epiglottic swelling, as determined by frequent examination using direct laryngoscopy or flexible fiberoptic laryngoscopy. In general, children with acute epiglottitis are intubated for 2–3 days, because the response to antibiotics is usually rapid. Most patients have concomitant bacteremia; occasionally, other infections are present, such as pneumonia, cervical adenopathy, or otitis media. Meningitis, arthritis, and other

invasive infections with *H. influenzae* type b are rarely found in conjunction with epiglottitis (but bacteremia is present).

Acute Infectious Laryngitis

Laryngitis is a common illness. Viruses cause most cases; diphtheria is an exception but is extremely rare in highly developed, industrialized countries (see Chapter 233). 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 years 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 other factors may also contribute.

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;brassy 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 hours, 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 four 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. Diphtheritic croup is extremely rare in North America and Europe, 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 293).

Sudden onset of respiratory obstruction can be caused by aspiration of a **foreign body** (see Chapter 435). The child is usually 6 months to 3 years 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 432). CT scans of the upper airway are helpful in evaluating for possible 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 either general anesthesia or respiratory failure, hypocalcemic tetany, infectious mononucleosis, trauma, and tumors or malformations of the larynx. A



Fig. 433.2 Epiglottitis in a 5-yr-old male with respiratory distress and drooling. A lateral soft tissue neck radiograph shows a markedly thickened epiglottis (white arrow), which is referred to as the “thumb” sign. The aryepiglottic folds (black arrow) also are thickened. (From Laya BF, Lee EY. Upper airway disease. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 51.2, p. 477.)

crouplike 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 toxin-producing *S. aureus* or *S. pyogenes*, toxic shock syndrome can develop. **Bacterial tracheitis** may have a biphasic illness, with the second phase after a crouplike illness associated with high fever, toxicity, and airway obstruction. Alternatively, the onset of tracheitis occurs without a second phase and appears as a continuation of the initial crouplike 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 during 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 hypoxemia. 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 the established treatment for moderate and 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 minutes. 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. Current evidence does not favor racemic epinephrine over L-epinephrine (5 mL of 1:1,000 solution) in terms of efficacy or safety.

The indications for the administration of nebulized epinephrine include moderate to severe stridor at rest, the possible need for intubation, respiratory distress, and/or hypoxemia. The duration of activity of racemic epinephrine is <2 hours. 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- to 3-hour period of observation provided they have no stridor at rest; have received steroids; and have normal air entry, normal pulse oximetry, and normal level of consciousness. Nebulized epinephrine should still be used cautiously in patients with tachycardia, heart conditions such as tetralogy of Fallot, and 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 antiinflammatory action. Oral steroids are beneficial, even in mild croup, as measured by improved symptoms at 2 hours, reduced return visits, 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 to a maximum dose of 16 mg; a dose as low as 0.15 mg/kg may be just as effective. More randomized controlled trials are needed to further evaluate the effectiveness of lower dose dexamethasone compared to 0.6 mg/kg. Prednisolone at a dose of 1 mg/kg has also been found to be noninferior to standard and low-dose dosing of dexamethasone. Intramuscular dexamethasone and nebulized budesonide

have an equivalent clinical effect; oral dosing of dexamethasone is as effective as intramuscular administration. 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 6 years 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, hypoxemia, cyanosis, depressed mental status, poor oral intake, persistent moderate croup symptoms (stridor and/or retractions at rest without agitation) after 4 hours after one dose of nebulized epinephrine and systemic glucocorticoids requiring more than one dose of nebulized epinephrine, 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. Ceftriaxone (dose 100 mg/kg/24 hr in one or two divided doses) plus vancomycin (dose 15 mg/kg/24 hr every 8 hours) 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 if a child within the home is younger than 4 years of age and incompletely immunized, is younger than 12 months of age and has not completed the primary vaccination series, or is immunocompromised.

Acute laryngeal swelling on an **allergic basis** responds to epinephrine (1 mg/mL concentration, previously referred to as 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 190). Corticosteroids may be considered, although there is little evidence of benefit (1–2 mg/kg/24 hr of prednisone for 1–2 days). However, patients who require hospitalization or have a history of asthma may benefit from corticosteroids. 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 epiglottitis has decreased 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, less often, tracheotomy is required for most patients with bacterial tracheitis and all young patients with epiglottitis. 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 86). 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 tracheostomy 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 hours. Racemic epinephrine and dexamethasone (0.5 mg/kg/dose 6–12 hr before extubation with a maximum dose of 16 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.

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433.2 Bacterial Tracheitis

Kristine Knuti Rodrigues and Genie E. Roosevelt

Bacterial tracheitis is an acute bacterial infection of the upper airway that is potentially life-threatening. *S. aureus* (see Chapter 227.1) is the most commonly isolated pathogen, with isolated reports of methicillin-resistant *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *Moraxella catarrhalis*, and nontypable *H. influenzae*; anaerobic organisms have also been implicated. The mean age is between 5 and 7 years. There is a slight male predominance. Bacterial tracheitis often follows a viral respiratory infection (especially laryngotracheitis or influenza virus infection), 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 metallic;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, with younger patients 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. 433.3); purulent material is noted below the cords during endotracheal intubation (Fig. 433.4).

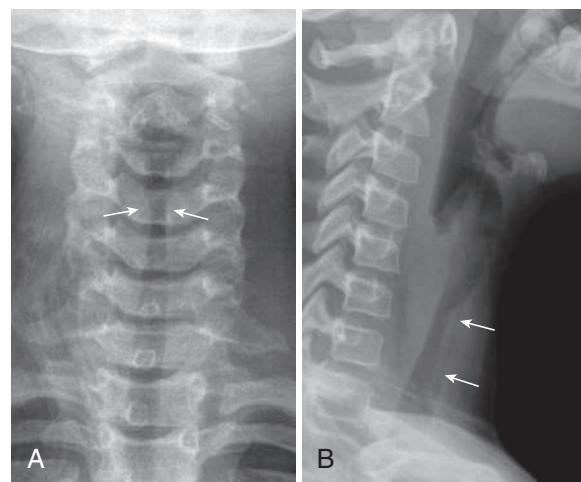


Fig. 433.3 Bacterial tracheitis in a 9-yr-old female with a high fever, cough, and stridor. A, Frontal soft tissue neck radiograph shows subglottic tracheal narrowing (arrows). B, Lateral soft tissue neck radiograph shows irregular linear membranous debris within the trachea (arrows). (From Laya BF, Lee EY. Upper airway disease. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 51.9, p. 481.)

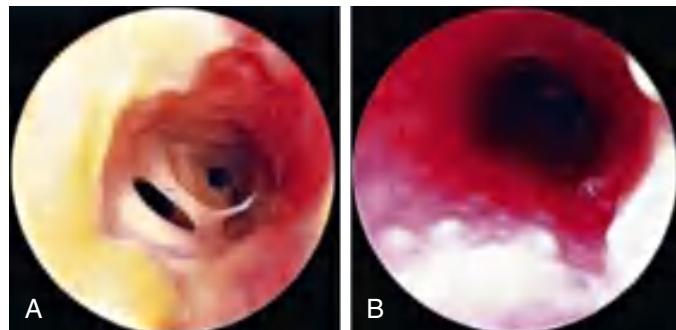


Fig. 433.4 Thick tracheal membranes seen on rigid bronchoscopy. The supraglottis was normal. A, Thick adherent membranous secretions. B, The distal tracheobronchial tree is unremarkable. In contrast to croup, tenacious secretions are seen throughout the trachea, and in contrast to bronchitis, the bronchi are not affected. (From Salamone FN, Bobbitt DB, Myer CM, et al. Bacterial tracheitis reexamined: is there a less severe manifestation? *Otolaryngol Head Neck Surg*. 2004;131:871–876. Copyright 2004 American Academy of Otolaryngology–Head and Neck Surgery Foundation, Inc.)

TREATMENT

Appropriate antimicrobial therapy, which usually includes anti-staphylococcal agents, should be instituted in any patient whose course suggests bacterial tracheitis. Empiric therapy recommendations for bacterial tracheitis include vancomycin or clindamycin and a third- or fourth-generation cephalosporin (e.g., ceftriaxone or cefepime). When bacterial tracheitis is diagnosed by direct laryngoscopy or is highly 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 227.2).

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.

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The timing of noisy breathing in relation to the sleep-wake cycle is important. Obstruction of the pharyngeal airway (by enlarged tonsils, adenoids, pharyngeal soft tissue, 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.

With airway obstruction, the degree of the obstructing lesion and the resulting work of breathing determine the necessity for diagnostic procedures and surgical intervention. Obstructive symptoms vary from mild to severe stridor or stridor with episodes of apnea, cyanosis, suprasternal (tracheal tugging) and subcostal retractions, dyspnea, and tachypnea. Significant congenital anomalies of the trachea and bronchi can create serious respiratory difficulties from the first minute of life and may sometimes be diagnosed in the prenatal period. If a severe obstruction is suspected prenatally, an airway birth plan should be developed by a high-risk maternal–fetal medicine expert, a neonatologist, and a pediatric airway surgeon. *Congenital high airway obstruction syndrome, or CHAOS, can lead to immediate postnatal distress (see Chapters 117 and 118).* Chronic obstruction can cause failure to thrive and chronic hypoxemia and may have long-term effects on growth and development.

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434.1 Laryngomalacia

Michael Gorelik and James W. Schroeder Jr.

Laryngomalacia accounts for 45–75% of congenital laryngeal anomalies in children with stridor. Stridor is inspiratory and can vary from high- to low-pitched. It can be present at rest 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, which creates a narrow airway and turbulent airflow. Symptoms usually appear within the first 2 weeks and increase in severity for up to 6 months, although gradual improvement can begin at any time. Many infants who do not require surgical intervention often have spontaneous resolution of stridor around 7–9 months of age, and the majority will have complete resolution of stridor by 18 months of age. Gastroesophageal reflux disease, laryngopharyngeal reflux disease, and neurologic disease with associated muscle hypotonia can influence the severity of the disease and thereby the clinical course.

DIAGNOSIS

The diagnosis is made primarily based on clinical symptoms and is confirmed by outpatient, awake flexible laryngoscopy (Fig. 434.1). 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 (FEES) 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. Laryngopharyngeal reflux is managed with antireflux medications, such as histamine H₂-receptor antagonists or proton pump inhibitors (PPIs).

Chapter 434

Congenital Anomalies of the Larynx, Trachea, and Bronchi

Michael Gorelik and James W. Schroeder Jr.

The larynx functions as a breathing passage, a valve to protect the lungs during swallowing, and the primary organ of communication. Symptoms related to congenital anomalies of the larynx include airway obstruction, noisy breathing, difficulty feeding, and abnormalities of phonation (see Chapter 421). Obstructive congenital lesions of the upper airway create turbulent airflow according to the laws of fluid dynamics. Turbulent airflow across a narrowed segment of the respiratory tract produces distinctive sounds that are diagnostically useful. The location of the obstruction produces characteristic changes in the sound of inspiration and/or expiration. Intrathoracic lesions typically cause expiratory wheezing and/or stridor, often masquerading as asthma or other pulmonary processes. 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 soft tissue from nasal or nasopharyngeal obstruction.

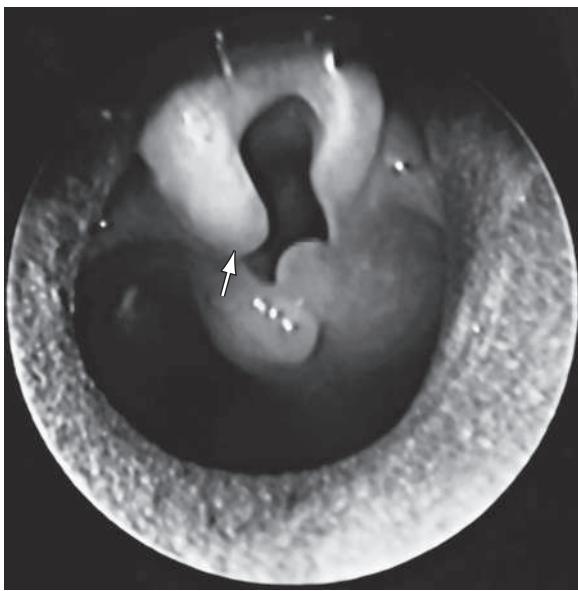


Fig. 434.1 Endoscopic example of laryngomalacia. On inspiration, the epiglottic folds collapse into the airway. The lateral tips of the epiglottis are also collapsing inward (arrow). (From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008.)

The risk-to-benefit ratio should be assessed in each patient because these medications, particularly PPIs, have been associated with iron-deficiency anemia and increased incidence of pneumonia, gastroenteritis, and *Clostridium difficile* infections, among others. In 15–20% of patients with laryngomalacia, symptoms are severe enough to cause progressive respiratory distress, cyanosis, failure to thrive, or cor pulmonale. In these patients, surgical intervention via supraglottoplasty is considered. Supraglottoplasty is 90% successful in relieving upper airway obstruction caused by laryngomalacia. Some comorbidities, such as cardiac disease, neurologic disease, pulmonary disorders, or craniofacial anomalies, may be poor prognostic indicators that would suggest earlier intervention.

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434.2 Congenital Subglottic Stenosis

Michael Gorelik and James W. Schroeder Jr.

Congenital subglottic stenosis is the second most common cause of stridor. The subglottis is the narrowest part of the upper airway in a child and is located in the space extending from the undersurface of the true vocal folds to the inferior margin of the cricoid cartilage. Subglottic stenosis is a narrowing of the subglottic larynx and in a term newborn is defined as a cricoid diameter of less than 3.5 mm resulting from malformation of the cricoid cartilage. Subglottic stenosis manifests in the infant with respiratory distress and biphasic or primarily inspiratory stridor. It may be congenital or acquired. Symptoms may present spontaneously with a higher degree of stenosis but manifest after a respiratory tract infection because of edema and thickened secretions of a narrow and already compromised airway leading to recurrent or persistent crouplike symptoms.

Biphasic or primarily inspiratory stridor is the typical presenting symptom for congenital subglottic stenosis. In a child with recurrent bronchiolitis or croup, a diagnosis of congenital subglottic stenosis should be considered. The stenosis can be caused by an abnormally shaped elliptical cricoid cartilage; by a first tracheal ring that becomes trapped underneath the cricoid cartilage; or by soft tissue thickening caused by ductal cysts, submucosal gland hyperplasia, or fibrosis.

Acquired subglottic stenosis refers to stenosis caused by extrinsic factors, most commonly resulting from prolonged intubation, and is discussed in further detail in Chapter 436.

DIAGNOSIS

The diagnosis made by airway radiographs is confirmed by direct laryngoscopy and bronchoscopy. During diagnostic laryngoscopy, the subglottic larynx is visualized directly and sized objectively using endotracheal tubes (Fig. 434.2). 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. Subglottic stenosis is typically measured using the Myer-Cotton system, with grade I through grade IV subglottic stenosis indicating the severity of narrowing. Other factors to consider aside from the degree of narrowing are whether the stenotic segment is soft or firm, which can determine the appropriate type of surgical intervention. Dilatation and endoscopic laser surgery can be attempted in grade I and II, although they may not be effective because most congenital stenoses are cartilaginous. Anterior cricoid split, anterior-posterior cricoid split, tracheostomy, or laryngotracheal reconstruction with cartilage graft augmentation are surgical options typically reserved for grade III and IV subglottic stenosis. The differential diagnosis includes other anatomic anomalies, as well as a subglottic hemangiomas or respiratory papillomatosis.

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434.3 Vocal Cord Paralysis

Michael Gorelik and James W. Schroeder Jr.

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 Chiari malformation, myelomeningocele, and hydrocephalus or birth trauma may be associated with bilateral paralysis. Additionally, congenital anomalies of the heart or great vessels can be associated with vocal cord paralysis. Bilateral vocal cord paralysis produces airway obstruction at the level of the glottis and is manifested by respiratory distress and high-pitched inspiratory stridor, aphonia or dysphonic sound, or inspiratory weak cry. More than 50% of cases of vocal cord paralysis in children are bilateral.

Unilateral vocal cord paralysis is most often iatrogenic, as a result of surgical treatment for aerodigestive (tracheoesophageal fistula) and cardiovascular (patent ductus arteriosus repair) anomalies and thyroid or parathyroid surgery, although it may also be idiopathic. Unilateral paralysis can lead to aspiration, coughing, and choking. Often the cry is weak and breathy, whereas stridor and other symptoms of airway obstruction are less common. Vocal cord paralysis in older children may be the result of a Chiari malformation or tumors compressing the vagus or recurrent laryngeal nerve. Vocal cord paralysis/palsies have also been reported in patients with Guillain-Barré syndrome (GBS) and its Miller Fisher variant either as an isolated finding or associated with other features of GBS. Other neurologic disorders producing vocal cord paralysis include stroke, multiple sclerosis, and other polyneuropathies. The prognosis for spontaneous recovery is better for unilateral, acquired, and right-sided paralysis.

DIAGNOSIS

The diagnosis of vocal cord paralysis is made by awake flexible laryngoscopy. The examination will demonstrate an inability or weakness to abduct the involved vocal cord. A thorough investigation for the underlying primary cause is indicated. Because of the association with other congenital lesions, evaluation includes neurology and cardiology consultations, imaging of the course of the recurrent laryngeal nerve, and diagnostic endoscopy of the larynx, trachea, and bronchi. During endoscopy, it is critical to palpate the cricoarytenoid joint to rule out joint fixation, which can be

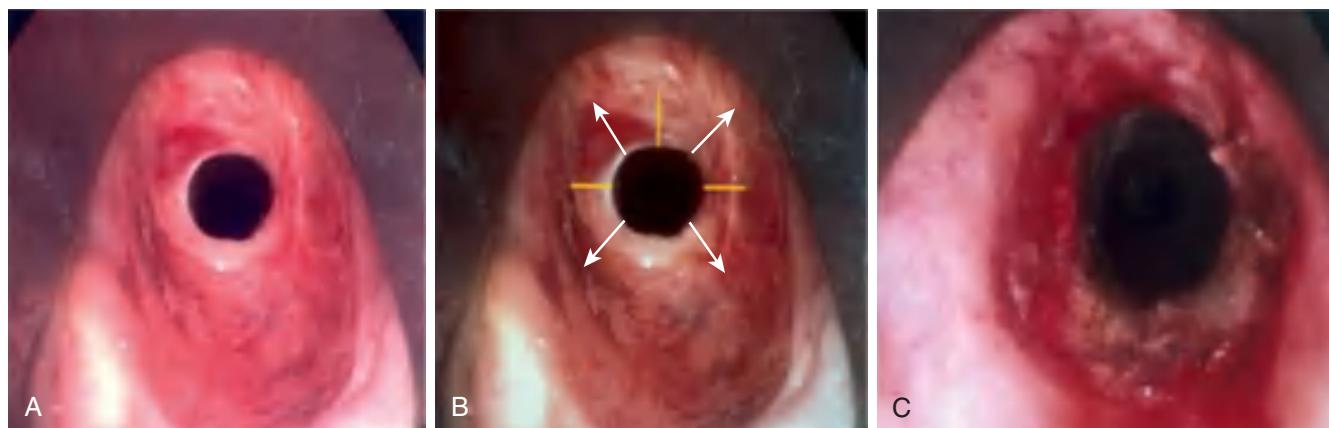


Fig. 434.2 Endoscopic repair of subglottic stenosis with radial cuts at 12, 3, and 9 o'clock positions using a laryngeal sickle knife or laser. A, Preoperative view. B, Diagram of planned incisions. C, After cuts and balloon dilation. (From Lawlor CM, Rahbar R, Choi SS. Glottic and subglottic stenosis and related voice disorders. In: Lesperance MM, ed. Cummings Pediatric Otolaryngology, 2nd ed. Philadelphia: Elsevier; 2022: Fig. 28.8, p. 409.)

mistaken for bilateral vocal fold paralysis. Intraoperative laryngeal electromyography (EMG) is the most specific and sensitive test to determine the presence of vocal cord paralysis.

TREATMENT

Treatment is based on the severity of the symptoms. Idiopathic vocal cord paralysis in infants usually resolves spontaneously within 6–12 months. If it is not resolved by 2–3 years of age, function typically does not recover. Patients with unilateral vocal cord paralysis often do not require intervention secondary to spontaneous recovery or compensation for the contralateral vocal cord. If there is persistent dysphonia or aspiration, surgical options include vocal fold injection, surgical medialization, or reinnervation using the ansa cervicalis, which has been successful in regaining unilateral vocal cord function. Postoperative voice therapy is helpful to achieve optimum results.

Bilateral paralysis may require temporary tracheotomy in 50% of patients. Airway augmentation procedures in bilateral vocal cord paralysis typically focus on widening the posterior glottis, such as an endoscopically placed or open posterior glottis cartilage graft, arytenoectomy, or arytenoid lateralization, sometimes in conjunction with cordotomy. These procedures are generally successful in reducing the obstruction; however, they may result in dysphagia and aspiration.

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434.4 Congenital Laryngeal Webs and Atresia

Michael Gorelik and James W. Schroeder Jr.

Congenital laryngeal webs account for about 5% of congenital laryngeal anomalies. They are typically located in the anterior glottis with subglottic extension and associated subglottic stenosis. During early embryogenesis, laryngeal webs form if the laryngotracheal lumen fails to fully recannulate. The clinical presentation ranges from asymptomatic, to dysphonia, to severe airway compromise secondary to the degree of obstruction caused by the web. Laryngeal webs are categorized from type I to type IV, which is the most severe.

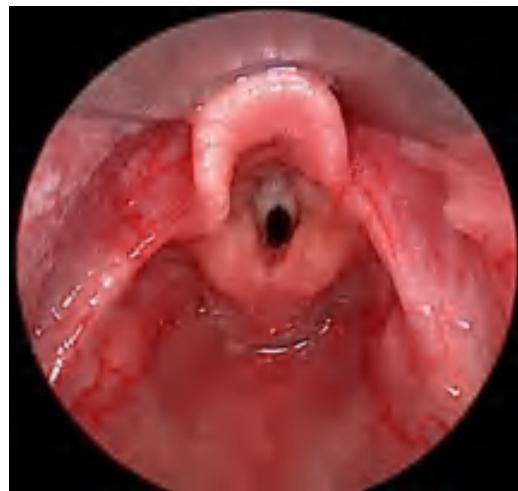


Fig. 434.3 Anterior glottic web, endoscopic view. (Courtesy Dr. Jeff Rastatter, Division of Pediatric Otolaryngology, Lurie Children's Hospital, Chicago, IL.)

Laryngeal atresia occurs as a complete glottic web due to failure of laryngeal and tracheal recanalization and may be associated with tracheal agenesis and tracheoesophageal fistula. Laryngeal atresia may be detected in the prenatal period, and preparations should be made for establishment of definitive airway, either before or at birth. Other times, congenital laryngeal atresia is a cause of respiratory distress in the newborn and is diagnosed only upon initial direct laryngoscopy.

Diagnosis is made by direct laryngoscopy (Fig. 434.3). Thick webs may be suspected in lateral radiographs of the airway. Chromosomal and congenital cardiovascular anomalies, as well as chromosome 22q11 deletion, are common in patients with laryngeal webs. Treatment may require only incision or dilation for thin webs. Thick webs can require laryngofissure and temporary stenting. Webs with associated subglottic stenosis are likely to require cartilage augmentation of the cricoid cartilage (laryngotracheal reconstruction). Voice outcomes are variable after surgical management.

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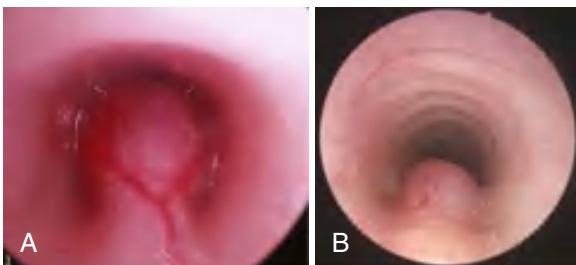


Fig. 434.4 A and B, Case of tracheal hemangioma prepropranolol and postpropranolol therapy (pictures 2 weeks apart). (From Bush A, Abel R, Chitty L, et al. Congenital lung disease. In: Wilmott RW, Deterding RR, Li A, et al., eds. Kendig's Disorders of the Respiratory Tract in Children, 9th ed. Philadelphia: Elsevier; 2019: Fig. 18.18, p. 308.)

434.5 Congenital Subglottic Hemangioma

Michael Gorelik and James W. Schroeder Jr.

See also Chapter 438.3.

Subglottic infantile hemangiomas are benign vascular malformations and a rare cause of early infancy respiratory distress. They present more commonly in females than in males, with symptoms of a barking cough and inspiratory or biphasic stridor in the absence of dysphonia. Symptoms typically present within the first 1–6 months of life. The most common presenting symptom is biphasic stridor, somewhat more prominent during inspiration. This is exacerbated by crying and acute viral illnesses. A barking cough, hoarseness, and symptoms of recurrent or persistent croup are typical and can mask the diagnosis. Roughly 50% of those with a subglottic hemangioma will have a cutaneous hemangioma, but only 1% of children who have cutaneous hemangiomas will have a subglottic hemangioma (see Chapter 691). However, a facial hemangioma in the beard distribution (preauricular area, lips, chin, and neck) is associated with a much higher incidence of subglottic hemangiomas and, when present, should prompt further investigation. Chest and neck radiographs can show the characteristic asymmetric narrowing of the subglottic larynx. CT and MRI can also assist with the diagnosis. Airway vascular lesions may also be associated with **PHACES syndrome**, characterized by posterior fossa malformations, hemangioma, arterial lesions of the head and neck, cardiac anomalies, eye anomalies, and sternal cleft (see Chapter 691). More than 50% of children with PHACES syndrome have an airway vascular lesion. Treatment options range from conservative monitoring, medical management, steroid injection, laser treatment, and open surgical resection to tracheotomy and airway reconstruction. Propranolol has become a mainstay in initial therapy of subglottic hemangioma; however, it is estimated that up to 50% of patients with subglottic hemangioma may not have a long-term response to propranolol, indicating a need for close airway monitoring in these patients (Fig. 434.4). Treatment is further discussed in Chapter 438.3.

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Fig. 434.5 Endoscopic photograph of a saccular cyst. (From Ahmad SM, Soliman AMS. Congenital anomalies of the larynx. Otolaryngol Clin North Am. 2007;40:177–191, Fig. 3.)

to hoarseness and dyspnea. Laryngoceles may be confined to the larynx or extend into the neck and are described as internal, external, or both. A saccular cyst (congenital cyst of the larynx) is distinguished from the laryngocoele in that its lumen is isolated from the interior of the larynx and it contains mucus, not air. Saccular cysts can be located in the anterior and lateral portions of the glottis and supraglottis. In infants and children, laryngoceles cause hoarseness and dyspnea that may increase with crying. Saccular cysts may cause respiratory distress and stridor at birth and may require early airway intervention. Infection of saccular cysts can lead to rapid expansion and acute airway compromise. Intubation can be challenging because the supraglottic and laryngeal anatomy may be distorted. In addition, complete airway obstruction may occur on induction with neuromuscular blockade because of decreased laryngeal tone. A saccular cyst may be visible on radiography, but the diagnosis is made by laryngoscopy (Fig. 434.5). Needle aspiration of the cyst confirms the diagnosis but rarely provides a cure. Surgical excision is the therapy of choice for management of saccular cysts and laryngocoeles. Approaches include endoscopic CO₂ laser excision, endoscopic extended ventriculotomy (marsupialization or unroofing), or, traditionally, external excision.

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434.6 Laryngoceles and Saccular Cysts

Michael Gorelik and James W. Schroeder Jr.

Saccular cysts and laryngocoeles are uncommon etiologies of pediatric airway obstruction. A laryngocoele is an abnormal air-filled dilation of the laryngeal saccule that arises vertically between the false vocal cord, the base of the epiglottis, and the inner surface of the thyroid cartilage. As there is open communication with the laryngeal lumen when it intermittently fills with air, this can lead

434.7 Posterior Laryngeal Cleft and Laryngotracheoesophageal Cleft

Michael Gorelik and James W. Schroeder Jr.

The posterior laryngeal cleft is the result of a deficiency in the midline of the posterior larynx caused by a failure of fusion of the posterior cricoid lamina. This results in an abnormal communication between the posterior larynx and esophagus leading to aspiration. Posterior laryngeal clefts are categorized into four types depending how far inferiorly the cleft extends. A **type I cleft** extends to, but not beyond, the vocal cords. A **type II cleft** extends beyond the vocal cords to, but not through, the cricoid cartilage. A **type III cleft** extends through the cricoid cartilage into the cervical trachea. A

type IV cleft extends into the thoracic trachea. Laryngeal clefts can occur in families and are likely to be associated with tracheal agenesis, tracheoesophageal fistula, and multiple congenital anomalies, including Opitz-Frias syndrome, Townes-Brock syndrome, chromosome 1q43 deletion, trisomy 21, and Pallister-Hall syndrome.

Type I clefts may cause mild symptoms, but at least 60% of these will cause no symptoms and will not require surgical repair. Type I and, more commonly, type II clefts can present with feeding problems, recurrent aspiration, pneumonias, or respiratory complaints. Infants with type III and IV clefts will present more commonly in the newborn period with significant aspiration and respiratory distress.

Diagnostic workup includes an esophagogram, which is undertaken to evaluate the presence of aspiration or laryngeal penetration of ingested contrast material. A FEES exam may be undertaken by an otolaryngologist with the assistance of a speech-language and pathology team to observe patterns of liquid spillage during swallow and may identify a cleft. However, the gold standard of diagnosis remains operative laryngoscopy and bronchoscopy with palpation of the posterior larynx. This assists in determining the length of the cleft and guides treatment options.

Treatment is based on the cleft type and the symptoms; in general, a type I cleft may be managed endoscopically, whereas higher grades may require an open procedure. 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.

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434.8 Vascular and Cardiac Anomalies

Michael Gorelik and James W. Schroeder Jr.

Aberrant cardiopulmonary vascular anatomy may directly affect the trachea and bronchi, resulting in respiratory and feeding problems (Fig. 434.6). The aberrant innominate artery is the most common cause of secondary tracheomalacia (see Chapter 481). 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 most commonly treated expectantly because the problem is often self-limited.

The term *vascular ring* is used to describe vascular anomalies that result from abnormal development of the aortic arch complex. Vascular rings are categorized as complete or incomplete. Double aortic arch is the most common type of complete vascular ring, followed by right aortic arch with aberrant left subclavian artery and left ligamentum arteriosum. These account for more than 95% of complete rings. The double aortic arch encircles and compresses both the trachea and esophagus. With few exceptions, these patients are symptomatic by 3 months of age. Respiratory symptoms predominate, but dysphagia may be present. The diagnosis is established by barium esophagogram that shows a posterior indentation of the esophagus by the vascular ring (see Fig. 434.6). CT or MRI with angiography provides the cardiothoracic surgeon the information needed. Surgical treatment for symptomatic patients entails division of the vascular ring.

Other vascular anomalies include the pulmonary artery sling, which also requires surgical correction. The most common open

(incomplete) vascular ring is the left aortic arch with aberrant right subclavian artery. It is usually asymptomatic, although dysphagia lusoria has been described. This is characterized as dysphagia caused by an aberrant subclavian artery coursing behind the esophagus, leading to esophageal compression and difficulty with bolus transit.

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 causes compression of the left main bronchus. Surgical correction of the underlying pathology to relieve pulmonary hypertension relieves the airway compression.

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434.9 Tracheal Stenoses, Webs, and Atresia

Michael Gorelik and James W. Schroeder Jr.

Long-segment congenital tracheal stenosis with *complete* tracheal rings typically presents within the first year 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 (in ~30%) or other cardiac anomalies (in about 25%), which can occur in one third of patients to one fourth of patients, respectively. Bronchoscopy is the best method to define the degree and extent of the stenosis and the associated abnormal bronchial branching pattern. Care must be taken to avoid traumatic passage of a telescope or bronchoscope through a stenotic or edematous segment, as even minor mucosal trauma may precipitate complete airway obstruction. Treatment of clinically significant stenosis involves tracheal resection of short-segment stenosis, slide tracheoplasty for long-segment stenosis, or tracheal rings. Total autologous tracheal replacement is another option. Congenital soft tissue stenosis and thin webs are rare. Dilatation may be all that is required.

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434.10 Foregut Cysts

Michael Gorelik and James W. Schroeder Jr.

The embryologic foregut gives rise to the pharynx, lower respiratory tract, esophagus, stomach, duodenum, and hepatobiliary tract. Foregut duplication cysts arise if heterotopic rests of foregut-derived epithelium persist anywhere along this tract. Foregut duplications account for approximately one third of all duplications. 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 delineates the mass and, in the case of enteric cyst, the associated vertebral anomaly. The treatment of all foregut cysts is surgical excision.

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434.11 Tracheomalacia and Bronchomalacia

See Chapter 437.

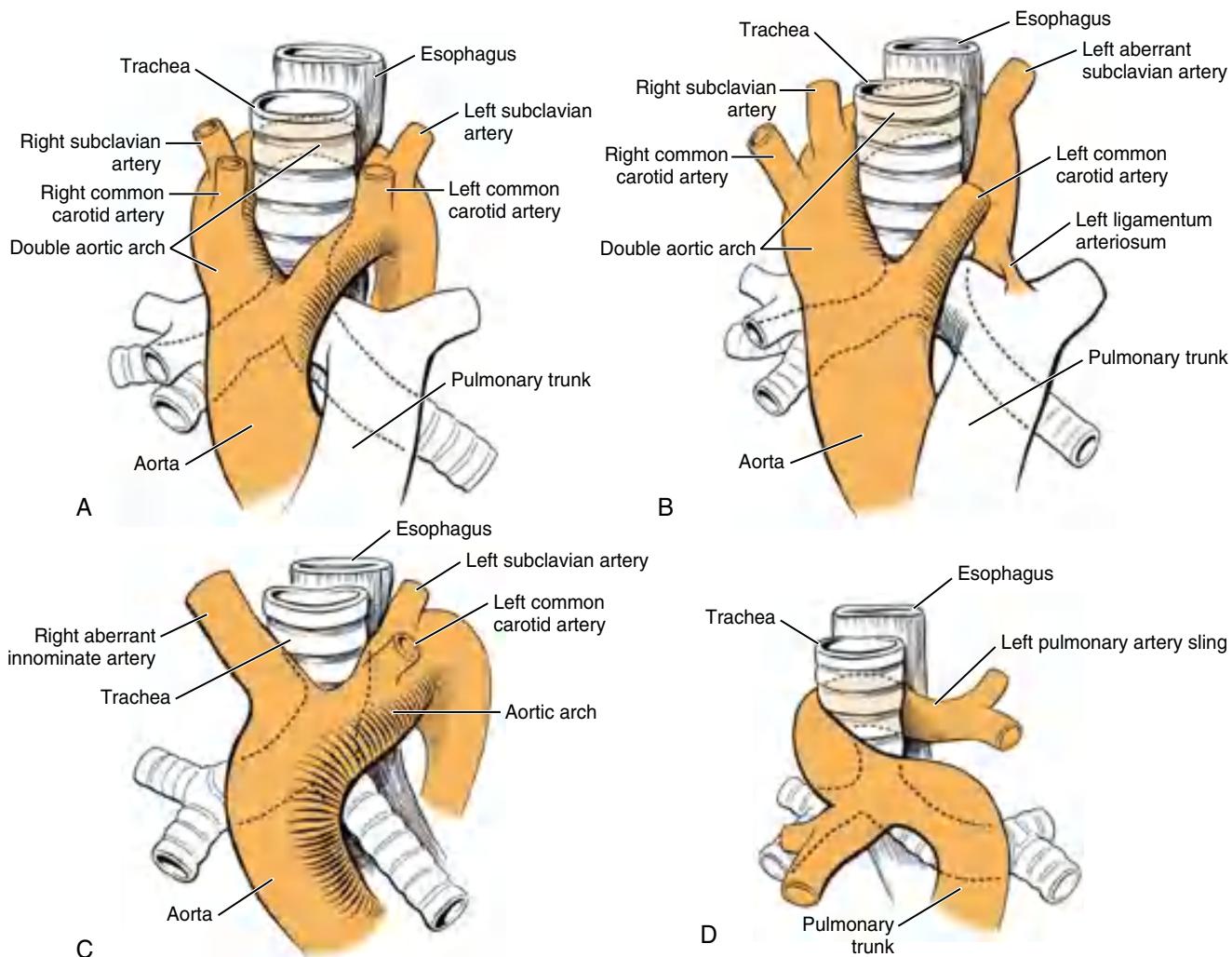


Fig. 434.6 Vascular rings. A, Double aortic arch. B, Right aortic arch with aberrant left subclavian artery and left ligamentum arteriosum. C, Aberrant innominate artery. D, Left pulmonary artery sling. (From Green GF, Ohye RG. Diagnosis and management of tracheal anomalies and tracheal stenosis. In: Lesperance MM, ed. Cummings Pediatric Otolaryngology, 2nd ed. Philadelphia: Elsevier; 2022: Fig. 30.6, p. 445.)

Chapter 435

Foreign Bodies in the Airway

Michael Gorelik and James W. Schroeder Jr.

Choking is a leading cause of morbidity and mortality among children, especially those younger than 4 years of age. From 2001 to 2009, an average of 12,435 children ages 0–14 years in the United States were treated in emergency departments for choking on food without fatality. The majority of children found to have foreign body aspiration are older infants and toddlers (Fig. 435.1), with males being 1.7 times more likely than females to aspirate a foreign body. Roughly 80% of airway foreign body aspirations occur in children younger than 3 years old, with a peak in incidence between ages 1 and 2. Food items ranging from nuts, seeds, popcorn, and food particles to hardware and pieces of toys account for 59.5–81% of all cases. Nonfood and inorganic objects such as coins, paper clips, pen caps, or small toys are more commonly

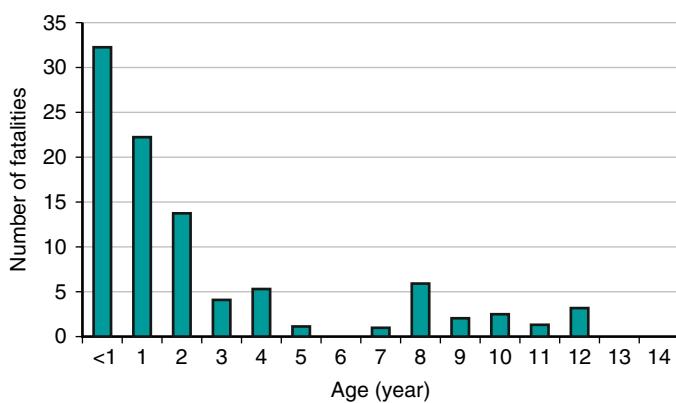


Fig. 435.1 Number of fatalities versus victim age, all fatality types. (From Milkovich SM, Altkorn R, Chen X, et al. Development of the small parts cylinder: lessons learned. *Laryngoscope*. 2008;118[11]:2082–2086.)

aspirated by older children. Globular, compressible, or round objects such as hot dogs, grapes, nuts, balloons, marshmallows, meats, and candies are particularly hazardous because of their ability to completely occlude the airway.

Younger children are at a higher risk for foreign body aspiration largely secondary to their developmental vulnerabilities and immature swallow function. Infants and toddlers often use their mouths to explore their surroundings, and children are more likely to be distracted, playing, or ambulatory while eating. Infants have the ability to suck and swallow and are equipped with basic involuntary reflexes (gag, cough, and glottis closure) that help to protect against aspiration during swallowing. Dentition develops at approximately 6 months of age with the eruption of the incisors, whereas molars do not erupt until approximately 1.5 years of age. Mature mastication takes longer to develop.

Despite these various protective mechanisms, a child's airway is more vulnerable to obstruction than an adult's airway. Young children are more likely to experience significant obstruction by small foreign bodies because of the smaller diameter of the pediatric airway. Mucus and secretions may form a seal around the foreign body, making it more difficult to dislodge by forced exhalation. In addition, the force of air generated by an infant's or young child's cough is less effective in dislodging an airway obstruction. For these reasons, it is recommended that children younger than 5 years of age avoid foods like hard candy or chewing gum and that raw fruits and vegetables be cut into small pieces. Additionally, children with developmental delays or neurologic and muscular disorders are at higher risk for foreign body aspiration.

CLINICAL MANIFESTATIONS

Foreign bodies of the airway have variable presentations and complications, depending on the characteristics, duration, and location of the foreign body. The clinical manifestations range from an asymptomatic state to severe respiratory distress. A high index of suspicion is often required, as delayed presentation is common, with more than 50% of cases presenting after 24 hours of the suspected aspiration event. The most serious complication of foreign body aspiration is complete obstruction of the airway, which may be recognized in the conscious child as sudden respiratory distress followed by an inability to speak or cough.

There are typically three stages of symptoms that result from aspiration of an object into the airway:

1. **Initial event:** Paroxysms of coughing, choking, gagging, and possible airway obstruction occur immediately after aspiration of the foreign body. This may be accompanied by tachypnea and stridor. The child is sometimes able to expel the foreign body during this stage.
2. **Asymptomatic interval:** The foreign body becomes lodged, reflexes fatigue, and the immediate irritating symptoms subside. The lack of symptoms can be particularly misleading to the provider when a child presents in this stage and accounts for a large percentage of delayed diagnoses and overlooked foreign bodies. Some patients with delayed presentation may eventually develop dyspnea, wheezing, or chronic cough.
3. **Complications:** Obstruction, erosion, or infection develops, which again directs attention to the presence of a foreign body. In this third stage, complications include fever, cough, hemoptysis, pneumonia, and atelectasis. Acute or chronic complications have been reported in almost 15% of cases of foreign bodies of the airway.

DIAGNOSIS

The clinical history is the most important factor in determining the need for operative bronchoscopy. A positive history must never be ignored, but a negative history can be misleading. Because nuts and seeds are the most common bronchial foreign bodies, the physician should specifically question the child's parents about these items, though it is important to keep in mind that aspiration events can be unwitnessed. Choking or coughing episodes accompanied by

new-onset wheezing and asymmetric breath sounds are highly suggestive of a foreign body in the airway, and bronchoscopy should be carried out promptly. A comprehensive physical exam is also essential, including examination of the nose, oral cavity, pharynx, neck, and lungs. Several reliable physical exam findings for airway foreign bodies include cough, decreased lung sounds, and wheezing. In addition to history and physical examination, radiology studies have an important role in diagnosing foreign bodies in the airway. Plain films are typically recommended first, although many foreign bodies are radiolucent (80–96%), and therefore providers often must rely on secondary findings (such as air trapping, asymmetric hyperinflation, obstructive emphysema, atelectasis, mediastinal shift, and consolidation) to indicate suspicion of a foreign body. Expiratory or lateral decubitus films can assist in revealing these suggestive secondary findings. The indication for computed tomography of the chest is currently being explored because of its high sensitivity and specificity, its ability to detect radiolucent objects, and its potential to eliminate the need for anesthesia and a procedure. However, with the known risks of radiation and the time-sensitive need for intervention, advanced imaging is rarely obtained. However, even in the absence of radiologic evidence on plain films, when the history and physical examination are suggestive of aspiration, bronchoscopy should be pursued.

TREATMENT

The treatment of choice for airway foreign bodies is prompt endoscopic removal with rigid instruments by a specialist (otolaryngologist or pulmonologist). Bronchoscopy is deferred only until providers have obtained preoperative studies and the patient has been prepared by adequate hydration and emptying of the stomach, though this can depend on the acuity of the clinical scenario. Airway foreign bodies are usually removed the same day the diagnosis is first considered. As with any treatment modality, providers must give careful consideration to the risks and benefits of the bronchoscopy procedure when the diagnosis is unclear. Potential complications of rigid bronchoscopy include bronchospasm, desaturation, bleeding, and airway edema; need for intubation; repeat procedures; and the inherent risks of anesthesia. Many surgeons maintain a lower threshold for intervention with the appropriate clinical history given the high risk of complications for a missed foreign body. Beyond the understanding of diagnosis and management of airway foreign bodies, there is a strong need and push for awareness, education, and prevention among caregivers, healthcare providers, and manufacturers of food and toys.

435.1 Laryngeal Foreign Bodies

Michael Gorelik and James W. Schroeder Jr.

Although laryngeal foreign bodies are less common (2–12% of cases) than bronchial or tracheal foreign bodies, they are particularly dangerous because of the risk of complete laryngeal obstruction, which can lead to asphyxiation unless it is promptly relieved with the Heimlich maneuver (see Chapter 79 and Figs. 79.6 and 79.7). As with airway foreign bodies in other locations, the presenting symptoms of laryngeal foreign bodies are determined by the size, shape, nature, and degree of obstruction. Objects that conform to the larynx can lead to complete obstruction, whereas with smaller objects the presentation can range from dysphonia, aphonia, stridor, cough, dyspnea, cyanosis, hemoptysis, and crouplike symptoms.

Clinical history is critical to establish an early diagnosis, and prompt intervention is critical.

435.2 Tracheal Foreign Bodies

Michael Gorelik and James W. Schroeder Jr.

Tracheal foreign bodies account for 3–12% of airway foreign body cases. Children who have tracheal foreign bodies can present with dysphonia, dysphagia, dry cough, or biphasic stridor. Posteroanterior and lateral soft tissue neck radiographs (airway films) are abnormal in 92% of children, whereas chest radiographs are abnormal in only 58% of these cases.

435.3 Bronchial Foreign Bodies

Michael Gorelik and James W. Schroeder Jr.

The majority of airway foreign bodies lodge in a bronchus (80–90% of cases) with a propensity to the right side. Occasionally, fragments of a foreign body may produce bilateral involvement or shifting infiltrates if

they move from lobe to lobe. Some children with bronchial foreign bodies present asymptotically, whereas others have asymmetric breath sounds, cough, and wheezing. Posteroanterior and lateral chest radiographs (including the abdomen) are standard in the diagnostic evaluation of infants and children suspected of having aspirated a foreign object. An 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 and air trapping. The persistent inflation of the obstructed lung causes a shift of the mediastinum toward the opposite side (Fig. 435.2). Air trapping is an immediate complication, whereas atelectasis is a late finding. Lateral decubitus chest films or fluoroscopy can provide the same information as expiratory films but are often unnecessary. Low-dose CT is considered by some a standard imaging study if previous conventional imaging is nondiagnostic. Clinical history and physical examination, not radiographs, ultimately determine the indication for bronchoscopy.

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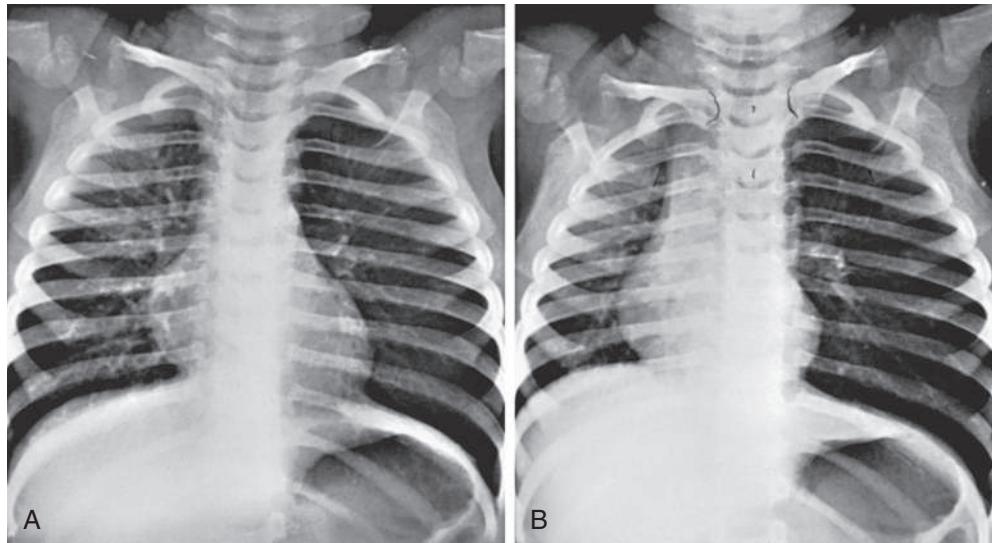


Fig. 435.2 A, Normal inspiratory chest radiograph in a toddler with a peanut fragment in the left main bronchus. B, Expiratory radiograph of the same child showing the classic obstructive emphysema (air trapping) on the involved (left) side. Air leaves the normal right side, allowing the lung to deflate. The medium shifts toward the unobstructed side.

Chapter 436

Laryngotracheal Stenosis and Subglottic Stenosis

Taher S. Valika and James W. Schroeder Jr.

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 compromised in most cases of laryngeal stenosis, particularly those that develop after 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 congenital when there is no other apparent cause such as a history of laryngeal trauma or intubation. Approximately 90% of cases manifest in the first year of life. Management relies on optimizing the airway, while ensuring the patient continues to grow. Knowledge of preventive measures is imperative to all healthcare members.

436.1 Congenital Subglottic Stenosis

See Chapter 434.2.

436.2 Acquired Laryngotracheal Stenosis

Taher S. Valika and James W. Schroeder Jr.

Ninety percent of acquired stenoses are a result of endotracheal intubation. The narrowest portion of the pediatric larynx is the subglottic region because of the narrow cricoid cartilage. When the pressure of the endotracheal tube against the cricoid mucosa is greater than the capillary pressure, ischemia occurs, followed by necrosis and ulceration. Secondary infection and perichondritis develop with exposure of cartilage (Fig. 436.1). Granulation tissue forms around the ulcerations. 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 is known to exacerbate 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, 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. Other presentations can also involve neonates who fail extubation, despite multiple attempts, and children with permanent dyspnea, stridor, or dysphonia.



Fig. 436.1 Bronchoscopy in a 2-mo-old infant showing mucosal erosion and cartilage exposure in the subglottic region. The child was intubated with an age-appropriate tube but with an excess of air in the cuff. (Courtesy Dr. Taher S. Valika, Division of Pediatric Otolaryngology, Ann & Robert H. Lurie Children's Hospital of Chicago.)

DIAGNOSIS

The diagnosis can be made by posteroanterior and lateral airway radiographs. The gold standard to confirm the diagnosis is via direct laryngoscopy and bronchoscopy in the operating room. High-resolution CT imaging and ultrasonography are of limited value. This is similar to the workup 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 reconstructive (expansion) surgery or resection of the narrowed portion of the laryngeal and tracheal airway (cricotracheal resection). Every effort is made to avoid tracheotomy using endoscopic techniques or open surgical procedures.

Fundamental knowledge of the airway can help reduce the incidence of stenoses. The use of age-appropriate tubes and cuffless tubes, treatment of gastroesophageal reflux, and reducing the duration of mechanical ventilation have led to an overall decrease in laryngotracheal stenoses in the past decade.

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Chapter 437

Bronchomalacia and Tracheomalacia

Jonathan D. Finder

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 437.1). Primary tracheomalacia and bronchomalacia are often seen in premature infants, although most affected patients are born at term. Secondary tracheomalacia and bronchomalacia refer to the situation in which the central airway is compressed by an adjacent structure (e.g., vascular ring; see Fig. 434.6) or is deficient in cartilage because of tracheoesophageal fistula (see Chapter 365). Bronchomalacia is common after lung transplantation, assumed to be secondary to the loss of bronchial artery supply leading to ischemia of the bronchial cartilage. This form of bronchomalacia may take months to

Table 437.1 Classification of Tracheomalacia

PRIMARY TRACHEOMALACIA

Congenital absence of tracheal-supporting cartilages

SECONDARY TRACHEOMALACIA

Esophageal atresia, tracheoesophageal fistula

Vascular rings (double aortic arch)

Tracheal compression from an aberrant innominate artery

Tracheal compression from mediastinal masses

Abnormally soft tracheal cartilages associated with connective tissue disorders

Prolonged mechanical ventilation, chronic lung disease

436.2 Acquired Laryngotracheal Stenosis

Taher S. Valika and James W. Schroeder Jr.

Ninety percent of acquired stenoses are a result of endotracheal intubation. The narrowest portion of the pediatric larynx is the subglottic region because of the narrow cricoid cartilage. When the pressure of the endotracheal tube against the cricoid mucosa is greater than the capillary pressure, ischemia occurs, followed by necrosis and ulceration. Secondary infection and perichondritis develop with exposure of cartilage (Fig. 436.1). Granulation tissue forms around the ulcerations. 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 is known to exacerbate 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, 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. Other presentations can also involve neonates who fail extubation, despite multiple attempts, and children with permanent dyspnea, stridor, or dysphonia.



Fig. 436.1 Bronchoscopy in a 2-mo-old infant showing mucosal erosion and cartilage exposure in the subglottic region. The child was intubated with an age-appropriate tube but with an excess of air in the cuff. (Courtesy Dr. Taher S. Valika, Division of Pediatric Otolaryngology, Ann & Robert H. Lurie Children's Hospital of Chicago.)

DIAGNOSIS

The diagnosis can be made by posteroanterior and lateral airway radiographs. The gold standard to confirm the diagnosis is via direct laryngoscopy and bronchoscopy in the operating room. High-resolution CT imaging and ultrasonography are of limited value. This is similar to the workup 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 reconstructive (expansion) surgery or resection of the narrowed portion of the laryngeal and tracheal airway (cricotracheal resection). Every effort is made to avoid tracheotomy using endoscopic techniques or open surgical procedures.

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Prolonged mechanical ventilation, chronic lung disease

present after transplantation. 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 one 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 has concurrent dysphagia with chronic aspiration, viral bronchiolitis, asthma, or other causes of peripheral airway 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) or in association with the loss of bronchial artery supply in lung transplantation. Persistent tracheomalacia is the rule after correction of tracheoesophageal fistula. Other causes of acquired tracheomalacia and bronchomalacia (especially left-sided) include cardiomegaly. The importance of the physical exam cannot be understated; one study found that pediatric pulmonologists made a correct assessment of malacia based on symptoms, history, and lung function before bronchoscopy in ~70% of cases. The cough in tracheomalacia and bronchomalacia can lead to collapse of the airway, which can lead to difficulty in airway clearance. The cough in tracheomalacia and bronchomalacia often has a barking, croupy quality. This can be managed in older patients with handheld positive expiratory pressure devices. Persistent cough in older children with tracheomalacia can cause irritation of the airway mucosa from the physical trauma and induce some degree of habitual cough.

DIAGNOSIS

Definitive diagnoses of tracheomalacia and bronchomalacia are established by flexible or rigid bronchoscopy (Fig. 437.1). The lesion is difficult to detect on plain radiographs. Although 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. Dynamic airway assessment using three-dimensional CT reconstruction at end-inspiration and end-expiration can be diagnostic and avoid the need for invasive evaluation. 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 caused by granulation tissue to erosion into adjacent vascular structures. Continuous positive airway pressure via tracheostomy may be indicated for severe cases. A 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. Reports of creation and use of three-dimensional (3D) printed, bioresorbable external tracheobronchial stents in pediatric patients with life-threatening tracheobronchomalacia have shown great promise.

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

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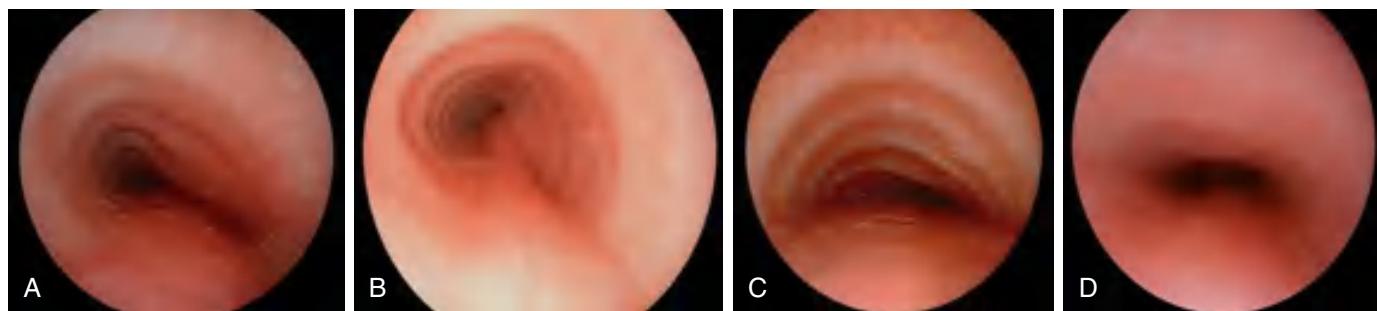


Fig. 437.1 Four examples of tracheomalacia appearances. A, Comma-shaped trachea caused by innominate artery compression requiring aortopexy. B, Bunched-up trachealis muscle and compressed trachea caused by a double aortic arch. C, Flattened trachea and increased trachealis diameter with a tracheoesophageal fistula in the posterior wall. D, Ovoid-shaped trachea from external compression by the innominate artery. (From Deacon JWF, Widger J, Soma MA. Paediatric tracheomalacia—a review of clinical features and comparison of diagnostic imaging techniques. *Int J Pediatr Otorhinolaryngol*. 2017;98:75–81.)

Chapter 438

Neoplasms of the Larynx, Trachea, and Bronchi

Saied Ghadersohi, Lauren D. Holinger, and James W. Schroeder Jr.

438.1 Vocal Nodules

Saied Ghadersohi and James W. Schroeder Jr.

Vocal nodules, which are not true neoplasms, are the most common cause of chronic hoarseness in children. Chronic vocal abuse or misuse (i.e., frequent yelling and screaming) produces localized vascular congestion, edema, hyalinization, and epithelial thickening in the bilateral vocal cords. This grossly appears as nodules that disrupt the normal vibration of the cords during phonation. Vocal abuse is the main factor, and the voice is worse in the evenings. The differential diagnosis can include unilateral lesions such as vocal cord cysts and polyps; however, these usually have an acute inciting event and are rarer in children.

Diagnosis is typically via laryngoscopy and stroboscopy to assess the characteristics of the bilateral nodules. Occasionally biopsy is needed in atypical-behaving/-appearing lesions. Treatment is primarily non-surgical, with voice therapy used in children >4 years of age who can participate in therapy and clinical monitoring with behavioral therapy in younger children or those with developmental delay. In addition, laryngopharyngeal reflux commonly exacerbates vocal abuse-induced irritation of the cord; therefore antireflux therapy can also be implemented (see Chapter 369). Surgical excision of vocal cord nodules in children is controversial and is rarely indicated but may be necessary if the child is unable to communicate adequately, becomes aphonic, or requires tension and straining to make an utterance.

438.2 Recurrent Respiratory Papillomatosis

Saied Ghadersohi and James W. Schroeder Jr.

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), most commonly types 6 and 11 (see Chapter 313). Seventy-five percent of recurrent respiratory papilloma (RRP) cases occur in children younger than age 5 years, but the diagnosis may be made at any age. In general, neonatal-onset disease is a poor prognostic factor with higher mortality and need for tracheostomy. Sixty-seven percent of children with RRP are born to mothers who had condylomas during pregnancy or parturition. The mode of HPV transmission is still not clear but is thought to be through exposure to HPV when traversing the birth canal of an infected mother. Other identified risk factors include first born, >10 hours of labor, and a young mother. However, HPV exposure is fairly common and RRP remains rare; additionally, in mothers with vaginal condylomata, only 1 in 231–400 vaginal births go on to develop respiratory papillomatosis. Therefore other risk factors contribute to transmission, and cesarean-section delivery for prevention cannot be recommended. However, preventive measures can include the prospective widespread use of the quadrivalent HPV vaccine to help eliminate maternal and paternal HPV reservoirs and possibly decrease cases of RRP caused by HPV-6 and -11.

CLINICAL MANIFESTATIONS

The clinical course involves remissions and exacerbations of recurrent papilloma, most commonly on the larynx (usually the vocal cords),

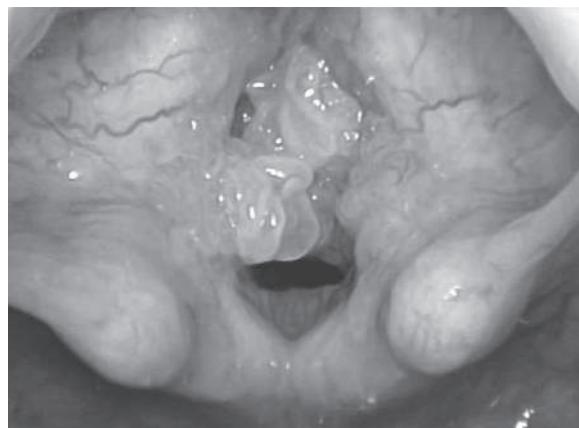


Fig. 438.1 Laryngoscopic view of respiratory papillomas causing near-complete obstruction at glottic level. (From Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. *Laryngoscope*. 2008;118:1236–1245.)

causing progressively worsening hoarseness, sleep-disordered breathing, exertional dyspnea, stridor, and, if left untreated, eventually severe airway obstruction (Fig. 438.1). Although it is a benign disease, lesions can spread throughout the aerodigestive tract in 31% of patients, most commonly the oral cavity, trachea, and bronchi. Rarely these lesions can undergo malignant conversion (1.6%); however, some patients may have spontaneous remission. Patients may be initially diagnosed with asthma, croup, vocal nodules, or allergies.

DIAGNOSIS AND TREATMENT

Diagnosis of RRP is via laryngoscopy and bronchoscopy. Biopsy should be obtained at the initial surgical intervention and regular intervals to rule out malignancy and to subtype the HPV, as it can affect prognosis. Treatment of RRP is endoscopic surgical removal with three goals. First, debulking/complete removal of the lesions; second, preservation of normal structures; and finally, prevention of scar formation in the affected areas. Most surgeons in North America prefer the microdebrider, although microsurgery, CO₂, and KTP laser techniques have been described. Despite these techniques, 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 four surgical procedures per year, rapid regrowth of papillomata with airway compromise, or distal multisite spread of disease. Adjunct therapies can be inhaled or administered intralesionally or systemically and include antiviral modalities (interferon, ribavirin, acyclovir, cidofovir), antiangiogenic agents such as bevacizumab (Avastin), photodynamic therapy, dietary supplement (indole-3-carbinol), non-steroidal antiinflammatory drugs (COX-2 inhibitors, Celebrex), retinoids, and mumps vaccination.

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438.3 Congenital Subglottic Hemangioma

Saied Ghadersohi and James W. Schroeder Jr.

See also Chapter 434.5.

Typically, congenital subglottic hemangiomas are symptomatic within the first 2 months of life, with almost all occurring before 6 months of age. Much like the cutaneous infantile hemangiomas, these lesions have two phases: a **proliferative phase** with rapid growth in the first 6 months of life and then they stabilize by 1 year and a slow **involution phase** typically by age 3. Patients present with usually inspiratory but sometimes biphasic stridor. The infant can have a barking cough and temporarily respond to steroids, similar to persistent croup. Fifty percent of congenital subglottic hemangiomas are associated

with facial lesions, but the converse is not true. Radiographs classically delineate an asymmetric subglottic narrowing. The diagnosis is made by direct laryngoscopy.

DIAGNOSIS AND TREATMENT

The diagnosis of subglottic hemangioma is based on history and laryngoscopic exam. MRI imaging with contrast can also be obtained to confirm the diagnosis of a vascular lesion. If the lesion does not respond to medical therapy, then biopsy (with GLUT1 staining; positive suggests hemangioma) may be indicated to rule out other vascular tumors. Subglottic hemangiomas are treated similarly to cutaneous hemangiomas (see Chapter 691). Propranolol is the first-line treatment of cutaneous and subglottic infantile hemangiomas. Typically, treatment is with 1-3 mg/kg/day of propranolol for 4-12 months (see Chapter 691). Prescreening patients with cardiology workup (i.e., electrocardiogram) is advised. Side effects include hypotension, bradycardia, bronchospasm, and hypoglycemia, which can be avoided by giving the medication with a feed.

There remains a role for systemic steroids, racemic epinephrine, and helium/oxygen treatment in the acute management of the airway and in lesions that are slow or nonresponsive to propranolol treatment (i.e., large hemangiomas with critical airway narrowing).

Surgical management is offered in severe cases or those not responsive to medical therapy. Interventions can range from intralesional steroid injection to avoid systemic steroid side effects, CO₂, or KTP laser endoscopic excision or open surgical excision, and ultimately as a last resort tracheostomy can establish a safe airway, allowing time for the lesion to involute per its natural course.

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438.4 Vascular Malformations

Saied Ghadersohi and James W. Schroeder Jr.

Based on the International Society for the Study of Vascular Anomalies classification system, these lesions can be classified into vascular malformations and vascular tumors. The most common vascular tumors are infantile/subglottic hemangiomas. Vascular malformations are not true neoplastic lesions. They have a normal rate of endothelial turnover and various channel abnormalities. They are subcategorized based on high or low flow and by their predominant type (capillary, venous, arterial, lymphatic, or a combination thereof). Overall, vascular malformations are uncommon, and they rarely occur in the larynx and airway. When they do occur, they are often an extension from elsewhere in the head and neck. It should be noted that these lesions can expand with a viral upper respiratory infection or hemorrhage into the lesion. They can be diagnosed with direct visualization during laryngoscopy or bronchoscopy or seen on CT/MRI imaging. Treatment usually entails a tailored multidisciplinary team approach with early surgery, laser resection, or sclerotherapy.

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438.5 Other Laryngeal Neoplasms

James W. Schroeder Jr. and Lauren D. Holinger

Neurofibromatosis (see Chapter 636.1) 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 549) 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.

438.6 Tracheal Neoplasms

Saied Ghadersohi, James W. Schroeder Jr., and Lauren D. Holinger

Tracheal tumors are extremely rare and include malignant and benign neoplasms; they may initially be misdiagnosed as asthma. The two 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. 438.2). 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. Treatment is based on the histopathology.

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438.7 Bronchial Tumors

Saied Ghadersohi and James W. Schroeder Jr.

Bronchial tumors are rare. In one series, carcinoid tumors were the most common, followed by mucoepidermoid and inflammatory pseudotumors. These patients can present with persistent pneumonia despite adequate treatment. The diagnosis is confirmed at bronchoscopy and biopsy; treatment depends on the histopathology.

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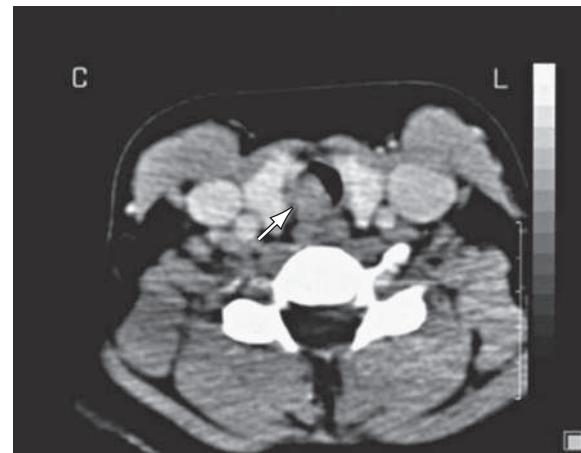


Fig. 438.2 CT scan of the trachea with a circumscribed intraluminal tracheal mass (arrow) in the tracheal wall. (From Venizelos I, Papathomas T, Anagnostou E, et al. Pediatric inflammatory myofibroblastic tumor of the trachea: a case report and review of the literature. *Pediatr Pulmonol*. 2008;43:831–835.)

Chapter 439

Wheezing, Bronchiolitis, and Bronchitis

439.1 Wheezing in Infants: Bronchiolitis

Samantha A. House and Shawn L. Ralston

Wheezing, the production of a musical continuous sound that originates in narrowed airways, is heard on expiration as a result of airway obstruction. Infants are more likely to wheeze than are older children as a result of differing lung mechanics. Obstruction of airflow is affected by both airway size and compliance of the infant lung. Resistance to airflow through a tube is inversely related to the radius of the tube to the fourth power. In children younger than 5 years, small-caliber peripheral airways can contribute up to 50% of the total airway resistance. Marginal additional narrowing, such as that caused by inflammation related to viral infection, is then more likely to result in wheezing.

Infant chest wall compliance is also quite high; thus the inward pressure produced in normal expiration subjects the intrathoracic airways to collapse. Differences in tracheal cartilage and airway smooth muscle tone increase the collapsibility of the infant airways in comparison with older children. These mechanisms combine to make the infant more susceptible to airway obstruction, increased resistance, and subsequent wheezing. The mechanical portion of the infant propensity to wheeze resolves with normal growth and muscular development.

Although wheezing in infants most frequently results from inflammation due to acute viral infections, there are many potential causes of wheezing (Table 439.1).

Acute Bronchiolitis

Acute bronchiolitis is a diagnostic term used to describe the clinical picture produced by multiple different viral lower respiratory tract infections in infants and very young children. The respiratory findings observed in bronchiolitis include tachypnea, wheezing, crackles, and rhonchi, which result from inflammation of the small airways (Fig. 439.1). Despite its commonality, a universal set of diagnostic criteria for bronchiolitis does not exist, with significant disagreement about the upper age limit for appropriate use of the diagnosis. Some clinicians restrict the term to children younger than 1 year, and others extend it to the age of 2 years or beyond.

The pathophysiology of acute bronchiolitis is characterized by bronchiolar obstruction with edema, mucus, and cellular debris (see Fig. 439.1). Resistance in the small air passages is increased during both inspiration and exhalation, but because the radius of an airway is smaller during exhalation, the resultant respiratory obstruction leads to expiratory wheezing, air trapping, and lung hyperinflation. If obstruction becomes complete, trapped distal air will be resorbed and the child will develop atelectasis. Hypoxemia may result from ventilation-perfusion mismatch. Hypercapnia may develop with severe obstructive disease.

Respiratory syncytial virus (RSV) is responsible for more than 50% of cases of bronchiolitis. Other causal agents include human metapneumovirus, rhinovirus, parainfluenza, influenza, coronavirus, bocavirus, and adenovirus, among others. Viral *co-infection* can occur; the impact of co-infection on severity and clinical manifestations of bronchiolitis remains unclear. Respiratory viruses can be identified in more than one third of asymptomatic patients younger than the age of 1 year, calling into question the specificity of nucleic acid amplification tests for active infection with some viruses. Although bacterial pneumonia is sometimes confused clinically with bronchiolitis, viral bronchiolitis is only rarely followed by bacterial superinfection.

Over 100,000 young children are typically hospitalized annually in the United States with the diagnosis of bronchiolitis, making it the most common diagnosis resulting in hospitalization for children younger

than 1 year of age in the United States over the past several decades. Hospitalization rates have been relatively stable in pre-COVID-19 pandemic years despite introduction and routine use of RSV immunoprophylaxis in selected high-risk populations. Nonetheless, variants of COVID-19 have been associated with a bronchiolitis-like syndrome. In addition, a robust RSV surge was observed in the late-pandemic period. Co-infection with COVID-19 has been observed,

Table 439.1 Differential Diagnosis and Etiologies of Wheezing in Infancy

INFECTIOUS
<i>Viral</i>
Respiratory syncytial virus
Human metapneumovirus
Parainfluenza
Adenovirus
Influenza
Rhinovirus
Bocavirus
Coronavirus, including COVID-19 variants
Enterovirus
<i>Other</i>
<i>Chlamydia trachomatis</i>
Tuberculosis
Histoplasmosis
Papillomatosis
ASTHMA
ANATOMIC ABNORMALITIES
<i>Central Airway Abnormalities</i>
Malacia of the larynx, trachea, and/or bronchi
Laryngeal or tracheal web
Tracheoesophageal fistula (specifically H-type fistula)
Laryngeal cleft (resulting in aspiration)
<i>Extrinsic Airway Anomalies Resulting in Airway Compression</i>
Vascular ring or sling
Mediastinal lymphadenopathy from infection or tumor
Mediastinal mass or tumor
Esophageal foreign body
<i>Intrinsic Airway Anomalies</i>
Airway hemangioma or other tumor
Congenital pulmonary airway malformation (cystic adenomatoid malformation)
Bronchial or lung cyst
Congenital lobar emphysema
Aberrant tracheal bronchus
Sequestration
Congenital heart disease with left-to-right shunt (increased pulmonary edema)
Foreign body
<i>Immunodeficiency States</i>
Immunoglobulin A deficiency
B-cell deficiencies
AIDS
Bronchiectasis
MUCOCILIARY CLEARANCE DISORDERS
Cystic fibrosis
Primary ciliary dyskinesia
Bronchiectasis
ASPIRATION SYNDROMES
Gastroesophageal reflux disease
Pharyngeal/swallow dysfunction
OTHER
Bronchopulmonary dysplasia
Eosinophilic granulomatosis with polyangiitis
Interstitial lung disease, including bronchiolitis obliterans
Heart failure
Anaphylaxis
Inhalation injury—burns

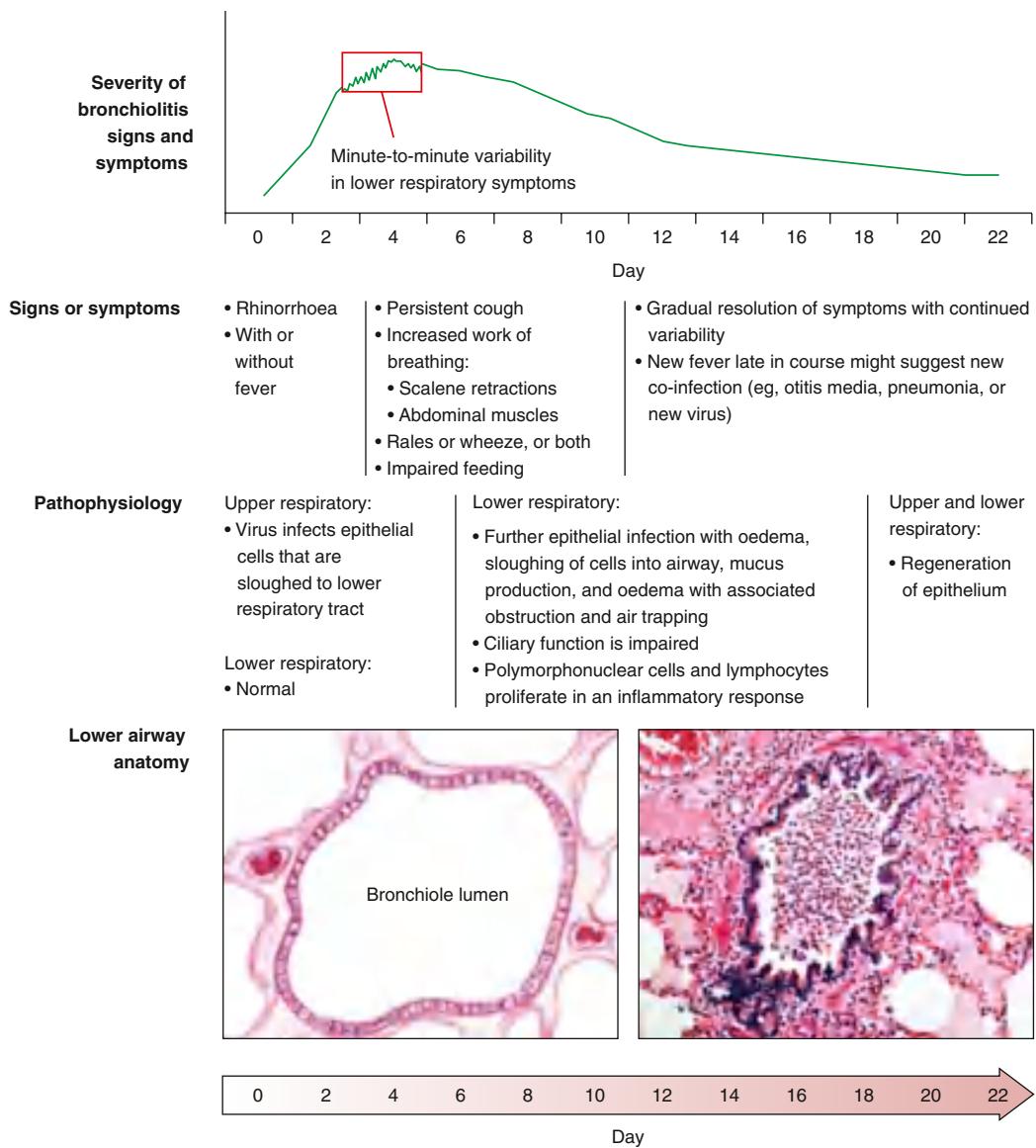


Fig. 439.1 Typical clinical course and pathophysiology of viral bronchiolitis. (From Florin TA, Plint PC, Zorc JJ. Viral bronchiolitis. Lancet. 2017;389:211–224, Fig. 1.)

but its implications on disease presentation and severity are not well characterized.

Bronchiolitis is more common in males, those exposed to second-hand tobacco smoke, those who have not been breastfed, and those living in crowded conditions. The risk is also higher for infants with mothers who smoked during pregnancy. Older family members, including older siblings, are a common source of infection; they might experience only minor upper respiratory symptoms (colds) given that bronchiolar edema may be less clinically apparent as airway size increases.

Asthma (see Chapter 185) is another important cause of wheezing, and the possibility of this diagnosis complicates the treatment of young children with bronchiolitis, although diagnosing asthma in the very young can be difficult. In prospective, longitudinal population cohort studies of infants, up to half of the cohort experienced a wheezing illness before school age, although when followed into adulthood only about 5–8% of patients prove to have asthma. In the largest U.S. cohort, three patterns of infant wheezing were proposed: transient early wheezing, comprising about 20% of the cohort, characterized by lower lung function at birth that improves with growth, resulting in resolution of wheezing by age 3; persistent

wheezing, comprising about 14% of the cohort, characterized by declining lung function and wheezing before and after age 3; and late-onset wheezing, comprising 15% of the cohort, characterized by relatively stable lung function and wheezing that does not begin until after age 3. The remaining 50% of the population did not suffer a wheezing illness. Following the cohort into adulthood revealed continued declines in the rates of persistent symptoms. Similar patterns are also seen in birth cohort studies in other countries.

Multiple studies attempting to predict which infants suffering from early wheezing illnesses will go on to have asthma in later life have failed to achieve discriminant validity. Interestingly, in both U.S. and UK prospective cohorts, wheezing with an onset *after* the first 18–36 months of life is one of the strongest predictors of eventual asthma in both cohorts. Other proposed 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, and peripheral eosinophilia, although no single factor is strongly discriminative. There is no evidence that early administration of systemic or inhaled corticosteroids to high-risk populations can prevent the development of asthma.

Table 439.2 Pertinent Medical History in the Wheezing Infant

Did the onset of symptoms begin at birth or thereafter?
Is the infant a noisy breather, and when is it most prominent?
Is the noisy breathing present on inspiration, expiration, or both?
Is there a history of cough apart from wheezing?
Was there an earlier lower respiratory tract infection?
Is there a history of recurrent upper or lower respiratory tract infections?
Have there been any emergency department visits, hospitalizations, or intensive care unit admissions for respiratory distress?
Is there a history of eczema?
Does the infant cough after crying or cough at night?
How is the infant growing and developing?
Is there associated failure to thrive?
Is there a history of electrolyte abnormalities?
Are there signs of intestinal malabsorption, including frequent, greasy, or oily stools?
Is there a maternal history of genital herpes simplex virus infection?
What was the gestational age at delivery?
Was the patient intubated as a neonate?
Does the infant bottle-feed in the bed or the crib, especially in a propped position?
Are there any feeding difficulties, including choking, gagging, arching, or vomiting with feeds?
Is there any new food exposure?
Is there a toddler in the home or lapse in supervision in which foreign body aspiration could have occurred?
Is there a change in caregivers or a chance of nonaccidental trauma?

Clinical Manifestations

The initial history of a wheezing infant should explore the onset, duration, and associated factors (Table 439.2), as well as *birth history* (weeks of gestation, neonatal complications including history of intubation or oxygen requirement, maternal complications) and prenatal smoke exposure. Past medical history, including any comorbid conditions, should be assessed. *Family history* of cystic fibrosis, immunodeficiencies, asthma in a first-degree relative, or any other recurrent respiratory conditions in children should be obtained. *Social history* should include any tobacco or other smoke exposure, daycare exposure, number of siblings, pets, and concerns regarding the 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.

Acute bronchiolitis is usually preceded by exposure (daycare, preschool, siblings) to contacts with a minor respiratory illness within the previous week (see Fig. 439.1). The infant first develops signs of upper respiratory tract infection with sneezing and clear rhinorrhea. This may be accompanied by diminished appetite and fever. Gradually, respiratory distress ensues, with paroxysmal cough, dyspnea, and irritability. The infant is often tachypneic, which can interfere with feeding. Though rare, apnea may occur in very young infants and may precede lower respiratory signs early in the disease. Infants at a postconceptual age of <44 weeks are at highest risk for *apneic* events, with premature birth providing an additional risk factor.

On physical examination, evaluation of the patient's vital signs with special attention to the respiratory rate and oxygen saturation is an important initial step. The exam is often dominated by wheezing and crackles. Expiratory time may be prolonged. 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.* Poorly audible breath sounds suggest severe disease with nearly complete bronchiolar obstruction.

Diagnostic Evaluation

Evaluation of wheezing in infancy and early childhood depends on suspected etiology. The diagnosis of **acute bronchiolitis** is clinical and should be considered in an infant presenting with a first episode of wheezing after a period of upper respiratory symptoms. Chest radiography is not routinely indicated in children with suspected bronchiolitis. Areas of atelectasis associated with bronchiolitis are often observed on chest radiographs and may be difficult to distinguish from bacterial pneumonia; as a result, obtaining chest radiography in a patient whose clinical course and exam are consistent with bronchiolitis may lead to unnecessary antibiotic use. Laboratory testing is also not routinely indicated; the white blood cell and differential counts are usually normal and are not predictive of bacterial superinfection. Viral testing (polymerase chain reaction or rapid immunofluorescence) is not routinely recommended in the diagnosis of bronchiolitis but may be helpful if such testing prevents more invasive evaluations or treatments. Concurrent serious bacterial infection (sepsis, pneumonia, meningitis) is unlikely, although confirmation of viral bronchiolitis may obviate the need for a sepsis evaluation in the young febrile infant. Otitis media may complicate bronchiolitis.

For young children with wheezing in whom the presentation does not clinically fit with the diagnosis of bronchiolitis, including those without other signs of viral infection, with very severe presentation, or with a complicated clinical course, further workup should be considered and should be dictated by individual clinical context. Children with recurrent or refractory episodes of wheezing in infancy, particularly if associated with failure to thrive, may require evaluation for chronic disorders such as cystic fibrosis or immunodeficiency.

Treatment

The treatment of children with viral bronchiolitis is supportive management. Those who are experiencing hypoxia, respiratory distress (inability to feed, extreme tachypnea, or significantly increased work of breathing), or apnea should be hospitalized. Risk factors for severe disease include younger age, preterm birth, or underlying comorbidity. Hypoxemic children should receive supplemental oxygen. There is a developing consensus surrounding target oxygen saturations; national guidelines in the United States propose a threshold of 90%. Oxygen can be administered via a number of delivery devices, and some children with severe disease may require positive pressure ventilation. High-flow nasal oxygen cannula (HFNC) use has become common, though studies to date have failed to demonstrate a consistent benefit on clinical outcomes. Despite an apparent stabilization with HFNC, such therapy has not consistently shortened the length of hospital stay or duration of oxygen therapy. Continuous pulse oximetry monitoring can be discontinued once patients are no longer requiring supplemental oxygen and are clinically improving.

Some children may also require support with supplemental hydration. Fluid can be administered intravenously or enterally via nasogastric tube, with some preference given to the latter because of an association between better outcomes with continued provision of enteral nutrition. If intravenous fluids are administered, care should be taken to use isotonic fluids because of the risk of hyponatremia. Frequent suctioning of nasal and oral secretions often provides relief of distress and improves work of breathing and ability to feed, although this should be limited to the nares or oropharynx because deep tracheal suctioning does not provide additional benefit and may cause harm. Chest physiotherapy has been extensively evaluated and provides *no benefit* to children with bronchiolitis.

Pharmacologic agents have largely proven *ineffective* in the management of bronchiolitis. Multiple systematic reviews and meta-analyses have failed to demonstrate any impact on clinical outcomes with use of albuterol or corticosteroids in bronchiolitis; neither are currently recommended for management. Response to bronchodilators is unlikely and unpredictable in children younger than 1 year. The use of inhaled or oral steroids in very young children with wheezing has not been shown to affect the disease trajectory or prevent the progression of childhood wheezing or development of asthma. There is debate over the use of

inhaled hypertonic saline in children with bronchiolitis, although most studies and meta-analyses fail to demonstrate any major benefit. Racemic epinephrine has not been found to improve the length of stay or clinical outcomes among inpatients with bronchiolitis, although there is some evidence to suggest that it may reduce the risk of hospitalization when used in the outpatient setting. Ribavirin, the only currently available antiviral medication targeting RSV, is also *not* currently recommended because of minimal impact on disease outcomes and because it is costly, difficult to administer, and associated with important toxicities.

PROGNOSIS

Infants with acute bronchiolitis are generally considered to be at highest risk for further respiratory compromise in the first 72 hours after onset of cough and dyspnea. The case fatality rate is <1% in developed countries, with death attributable to respiratory arrest and/or failure or severe dehydration and electrolyte disturbances. *A majority of deaths caused by bronchiolitis occur in children with complex medical conditions or comorbidities such as bronchopulmonary dysplasia, congenital heart disease, or immunodeficiency.* The median duration of symptoms in ambulatory patients is approximately 14 days; 10% may be symptomatic for 3 weeks. Severe lower respiratory tract infection at an early age has been identified as a possible risk factor for the development of asthma, although most children with early childhood wheezing will not go on to suffer from asthma. It is unclear whether viral infections causing bronchiolitis incite an immune response that manifests as asthma later in life or whether those infants have an inherent predilection for asthma that is first manifested as viral bronchiolitis.

PREVENTION (See also Chapter 307)

Meticulous hand hygiene is the best measure to prevent transmission of the viruses responsible for bronchiolitis. Nirsevimab, a one dose long-acting monoclonal antibody, is approved for prevention of RSV infection in newborns and infants. Nirsevimab is indicated for infants < 8 months of age born during or entering their first RSV season (in the continental US this may be October to March, although there may be regional differences), including those previously recommended to receive palivizumab (which is not given). Nirsevimab dose in the first RSV season is 50 mg if < 5 kg and 100 mg in infants ≥ 5 kg. In addition, older infants (8-19 months) who are at increased risk of severe RSV infection entering their second RSV season should also receive nirsevimab. These older infants include those with:

- Chronic lung disease of prematurity that requires chronic steroid or diuretic therapy or supplemental oxygen
- Severe immunocompromising conditions
- Cystic fibrosis with severe lung disease or poor weight gain
- American Indian and Alaska Native

The single dose of nirsevimab in the second RSV season is 200 mg given as two 100 mg injections in different sites. Nirsevimab may be co-administered with other routine childhood immunizations. Because of the availability of nirsevimab, immunization of high-risk populations with palivizumab is no longer recommended even if they received palivizumab in the previous RSV season.

In addition to immunization after birth, there is an FDA-approved maternal vaccine to prevent neonatal and infant RSV infections. The one dose vaccine (bivalent RSV prefusion F protein) is approved for use in women between 32-36 weeks' gestation. Nirsevimab is the only recommended approach to RSV prevention by the ACIP (CDC) and the AAP.

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439.2 Bronchitis

Samantha A. House and Shawn L. Ralston

Nonspecific bronchial inflammation is termed *bronchitis* and can occur in multiple childhood conditions. Acute bronchitis is a clinical syndrome, usually viral in origin, with cough as a prominent feature.

Acute tracheobronchitis is a term used when the trachea is prominently involved, such as with pertussis, parainfluenza, or diphtheria.

ACUTE BRONCHITIS

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 damaged or hypersensitized, leading to a protracted cough lasting 1-3 weeks.

The child first presents with nonspecific upper respiratory infectious symptoms, such as rhinitis. Three to four days later, a frequent, 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 thins, usually within 5-10 days, and then the cough gradually abates. The entire episode usually lasts about 2 weeks and seldom longer than 3 weeks.

Findings on physical examination vary with the age of the patient and stage of the disease. Early findings include no or 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 wheezing possible. Chest radiographs may be normal or may demonstrate increased bronchial markings.

The principal objective of the clinician is to exclude bacterial illnesses requiring antibiotic treatment, such as pneumonia, pertussis, or bacterial tracheitis. Obtaining sputum can be difficult in young children, and isolation of bacteria may not always indicate infection; thus sputum cultures are not generally recommended outside of specific diseases such as cystic fibrosis. Absence of vital sign abnormalities (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 439.3).

Table 439.3 Disorders with Cough as a Prominent Finding

CATEGORY	DIAGNOSES
Inflammatory	Asthma
Chronic pulmonary processes	Bronchopulmonary dysplasia Postinfectious bronchiectasis Cystic fibrosis Tracheomalacia or bronchomalacia Primary ciliary dyskinesia Other chronic lung diseases
Other chronic disease or congenital disorders	Laryngeal cleft Swallowing disorders Gastroesophageal reflux Airway compression (such as a vascular ring or hemangioma) Congenital heart disease
Infectious or immune disorders	Immunodeficiency Eosinophilic lung disease Tuberculosis Allergy Sinusitis Tonsillitis or adenoiditis <i>Chlamydia, Ureaplasma</i> (infants) <i>Bordetella pertussis</i> <i>Mycoplasma pneumoniae</i>
Acquired	Foreign body aspiration, tracheal or esophageal

Treatment

There is no specific therapy for acute bronchitis. The disease is typically a response to a viral infection and is self-limited. 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 are contraindicated in the youngest children, and although they may relieve symptoms, they can also increase the risk of superinfection and therefore should be used judiciously. Antihistamines and expectorants are not indicated. Nonprescription cough and cold medicines should not be used in children younger than 4 years of age, and their use is cautioned in children age 4-11 years.

CHRONIC BRONCHITIS

Chronic bronchitis is well recognized in adults, formally defined as 3 months or longer of productive cough each year for 2 or more years. The disease can develop insidiously, with episodes of acute obstruction alternating with quiescent periods. Some 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.

The applicability of this definition to children is unclear. The existence of chronic bronchitis as a distinct entity in children is controversial. Like adults, children with chronic inflammatory diseases or those with toxic exposures can develop damaged pulmonary epithelium. Thus chronic or recurring cough in children should lead the clinician to search for underlying pulmonary or systemic disorders (see Table 439.3). One proposed entity that shares characteristics with asthma and other forms of suppurative lung disease is persistent or protracted bacterial bronchitis. Protracted bacterial bronchitis is defined as three or more of the following criteria: (1) continuous wet or productive cough >4 weeks, (2) no signs or symptoms to suggest other causes, and (3) cough resolves with appropriate course of oral antibiotics.

CIGARETTE SMOKING AND AIR POLLUTION

Exposure to environmental irritants, such as tobacco smoke and air pollution, can incite or aggravate cough. There is a well-established association between tobacco exposure and pulmonary disease, including bronchitis and wheezing. This can occur through cigarette smoking or by exposure to secondhand smoke. Marijuana smoke, electronic cigarettes, and other inhalants are irritants sometimes overlooked when eliciting a history.

A number of pollutants compromise lung development and likely precipitate lung disease, including particulate matter, ozone, acid vapor, and nitrogen dioxide. Proximity to motor vehicle traffic is an important source of these pollutants. Because these substances coexist in the atmosphere, the relative contribution of any one to pulmonary symptoms is difficult to discern.

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Chapter 440

Plastic Bronchitis

Brett J. Bordini

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 a state of altered respiratory epithelial function and is most frequently encountered in the setting of underlying pulmonary or cardiac disease, although plastic bronchitis may also arise in lymphatic disorders, pulmonary infections, and the acute chest syndrome of sickle cell disease (Table 440.1). In

Table 440.1 Conditions Associated with Plastic Bronchitis	
PROVEN CONDITIONS	
Congenital heart disease with Fontan physiology	
Pulmonary lymphatic anomalies	
Influenza A pulmonary infection	
Adenovirus infection	
<i>Mycoplasma pneumoniae</i> infection	
POSSIBLE CONDITIONS	
Toxic inhalation	
Sickle cell acute chest syndrome	
Hypersecretory and near-fatal asthma (eosinophilic casts)	
Noonan syndrome	
UNLIKELY AND UNPROVEN CONDITIONS	
Bacterial pneumonia	
Bronchiectasis	
Cystic fibrosis	
Chronic obstructive pulmonary disease	
Nephrotic syndrome	

Modified from Rubin BK. Plastic bronchitis. *Clin Chest Med*. 2016;37:405–408, Box 1.



Fig. 440.1 Tracheobronchial casts after bronchoscopic extraction. Casts show branched architecture corresponding to the bronchial tree. (From Corrin B, Nicholson AG. *Pathology of the Lungs*, 3rd ed. London: Churchill Livingstone; 2011: Fig. 3.20.)

comparison with 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. 440.1). These casts may be spontaneously expectorated or may require bronchoscopic removal for relief of potentially fatal airway obstruction. Cast composition varies, although it 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, with an estimated prevalence of 6.8 cases per 100,000 pediatric patients. Prevalence varies according to the underlying associated disease with rates as high as 14% in patients who have undergone staged palliation of complex congenital heart disease and much lower rates in patients with 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. Children with single-ventricle Fontan physiology are at high risk for developing plastic bronchitis.

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 primarily of fibrin with neutrophilic or, more often, eosinophilic infiltration, and type 2 acellular casts, composed primarily of mucin with little to no cellular infiltration. Type 1 casts tend to be associated with inflammatory and infectious disorders of the lung, whereas type 2 casts tend to be associated with surgically palliated structural heart disease, particularly single-ventricle lesions. However, these distinctions are not absolute; patients with structural heart disease can have fibrin-predominant casts, and patients with asthma or atopic disease can have mucin-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 lymphatic drainage, particularly after staged surgical palliation. Under these circumstances, increased central venous pressure is believed to compromise the integrity of the bronchial mucosa, impeding lymphatic flow and resulting in the development of collateral lymphatic vessels and potentially of lymphoalveolar fistulae that may exude proteinaceous material into the airway lumen.

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 hypoxicemic or in severe respiratory distress. The expectoration of large, branched casts that are often tan in 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 have an associated risk of tracheobronchial cast formation, such as uncorrected or surgically palliated complex congenital heart disease (Fontan physiology); a history of atopic disease or asthma; lymphatic disorders such as Noonan syndrome, Turner syndrome, lymphangiectasia, and yellow nail syndrome; sickle cell disease; and infectious exposures, particularly to tuberculosis, adenovirus, influenza, 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 to allow for specific therapies directed at alleviating residual obstruction or 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, and if the predominant content of the cast is known, therapy with either fibrinolytics such as tissue plasminogen activator or mucolytics such as *N*-acetylcysteine or deoxyribonuclease may be considered as an adjunct to direct removal. Aerosolized heparin or mucolytics have also been used for treatment or prevention of recurrence, with varying success.

In the setting of inflammatory airway disease, additional preventive measures include inhaled or systemic corticosteroids, low-dose azithromycin, and leukotriene inhibitors to minimize airway inflammation. Bronchodilators have not been shown to prevent cast formation or aid in their removal, though may be used in the setting of concomitant bronchospasm.

In patients with surgically palliated complex congenital heart disease, measures aimed at decreasing central venous pressure, such as sildenafil or Fontan conduit fenestration, have had varied success. Lymphangiography may be undertaken to identify aberrant lymphatic vessels contributing to plastic bronchitis in the setting of congenital heart disease or lymphangitic disorders. MRI-guided selective lymphatic embolization of these channels has led to resolution of plastic bronchitis while preserving central lymphatic flow. Thoracic duct ligation has been helpful in patients in whom selective embolization has failed. Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus have been used to treat lymphatic malformations, with varying success. Octreotide and low-fat diets have demonstrated modest success in adult patients. Cardiac transplantation typically results in resolution of plastic bronchitis in the setting of repaired complex congenital heart disease.

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% to 50% in the setting of asthma or atopic disease and from 14% to 50% in the setting of complex congenital heart disease, with central airway obstruction leading to death in the majority of patients.

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Chapter 441

Emphysema and Overinflation

Steven R. Boas and Vicki K. Masson

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 distension 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 this resultant **unilateral hyperlucent lung** is quite broad and can involve the lung parenchyma, airways, pulmonary vasculature, chest wall (see Chapter 467), and mediastinum. Localized obstructions that can be responsible for overinflation include airway foreign bodies and the inflammatory reaction to them (see Chapter 435), abnormally thick mucus (cystic fibrosis, see Chapter 454), endobronchial tuberculosis or tuberculosi of the tracheobronchial lymph nodes (see Chapter 261), 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 after, most commonly, adenovirus (see Chapter 309) or respiratory syncytial virus (see Chapter 307), *Mycoplasma pneumoniae* (see Chapter 269), or measles (see Chapter 293). The infection can cause pulmonary vascular hypoplasia with resultant hypoperfusion, leading to unilateral hyperlucent lung (underdevelopment). Clinically, children with this condition often have chronic cough, recurrent pneumonia, hemoptysis, 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. Thoracoscopic evaluation may be useful. The triad of unilateral hyperlucent lung, diffusely decreased ventilation, and matching decreased perfusion of the affected lung supports 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. For those with recurrent infection or severe lung destruction, treatment may include immunization with influenza and pneumococcal vaccines, as well as surgical resection. However, without treatment, some individuals may become less symptomatic with time.

Congenital Lobar Emphysema (Congenital Large Hyperlucent Lobe)

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 (Table 441.1). 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 affect the left upper lobe. Extrapulmonary lesions are noted in Table 441.2.

Clinical manifestations usually become apparent in the neonatal period but are delayed for as long as 5–6 years in 5% of patients. Many cases are diagnosed by antenatal ultrasonography. Infants 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 one or more lobes;

Table 441.1 Etiology of Congenital Lobar Emphysema

1. Idiopathic (50%)
2. Bronchial cartilage absence, hypoplasia, or dysplasia (25%)
3. Parenchymal diseases
 - Polyalveolar lobe
 - Pulmonary alveolar glycogenosis
4. Internal bronchial obstruction
 - Bronchial stenosis
 - Bronchomalacia
 - Meconium aspiration
 - Hypertrophic mucosa membranes
 - Mold mucous plaques
 - Foreign body aspiration
 - Bronchial polyp
5. External bronchial obstruction
 - Pulmonary artery sling anomaly
 - Pulmonary rotation anomaly
 - Bronchogenic cyst
 - Lymphadenopathy
 - Mediastinal mass
 - Duplication of esophagus

From Demir OF, Hangul M, Kose M. Congenital lobar emphysema: diagnosis and treatment options. *J Chronic Obstr Pulm Dis*. 2019;14:921–928, Table 1. Originally published by and used with permission from Dove Medical Press Ltd.

Table 441.2 Concomitant Malformations Accompanying Congenital Lobar Emphysema

Cardiac malformations 14–20%	Patent ductus arteriosus Atrial septal defect Ventricular septal defect Tetralogy of Fallot Pulmonary stenosis Pulmonary valve atresia Aortic coarctation Pulmonary hypertension Left aortic arch Right descending aorta Left ligamentum arteriosum Double superior vena cava
Renal anomalies	Aplastic kidney Horseshoe kidney
Musculoskeletal anomalies	Pectus excavatum Hiatal hernia Diaphragmatic hernia
Gastrointestinal tract	Omphalocele Pyloric stenosis
Others	Cleft palate Chondroectodermal dysplasia Chondroostrophy Cystinosis Bronchial atresia Tracheal bronchus
Syndromes	Williams-Beuren syndrome Miller-Dieker syndrome Niemann-Pick disease Fanconi aplastic anemia

From Demir OF, Hangul M, Kose M. Congenital lobar emphysema: diagnosis and treatment options. *J Chronic Obstr Pulm Dis*. 2019;14:921–928, Table 2. Originally published by and used with permission from Dove Medical Press Ltd.

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, and atelectasis of the ipsilateral normal lung can ensue. With further distention, the mediastinum is shifted to the contralateral side, with impaired function seen as well

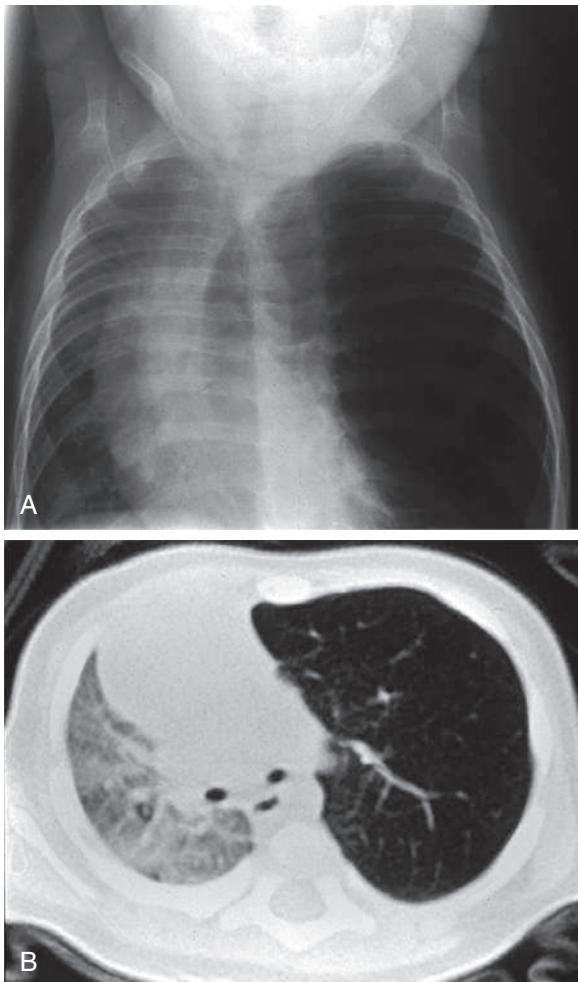


Fig. 441.1 Chest x-ray (A) and CT scan (B) of a congenital large hyperlucent lobe (congenital lobar emphysema). (From Bush A, Abel R, Chitty L, et al. Congenital lung disease. In: Wilmott RW, Deterding RR, Li A, et al., eds. Kendig's Disorders of the Respiratory Tract in Children, 9th ed. Philadelphia: Elsevier; 2019: Fig. 18.32.)

(Fig. 441.1). A radiolucent lobe and a mediastinal shift are often revealed by radiographic examination. A CT scan can demonstrate the aberrant anatomy of the lesion, and MRI or MR angiography can demonstrate any vascular lesions that might be causing extraluminal compression. Nuclear imaging studies are useful to demonstrate perfusion defects in the affected lobe. Figure 441.2 outlines the evaluation of an infant presenting with suspected CLE. The differential diagnosis includes pneumonia with or without an effusion, pneumothorax, and cystic adenomatoid malformation.

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.

Pulmonary Vascular Abnormalities

Unilateral hyperlucency may result from **unilateral pulmonary agenesis** (see Chapter 444) 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 481), also known

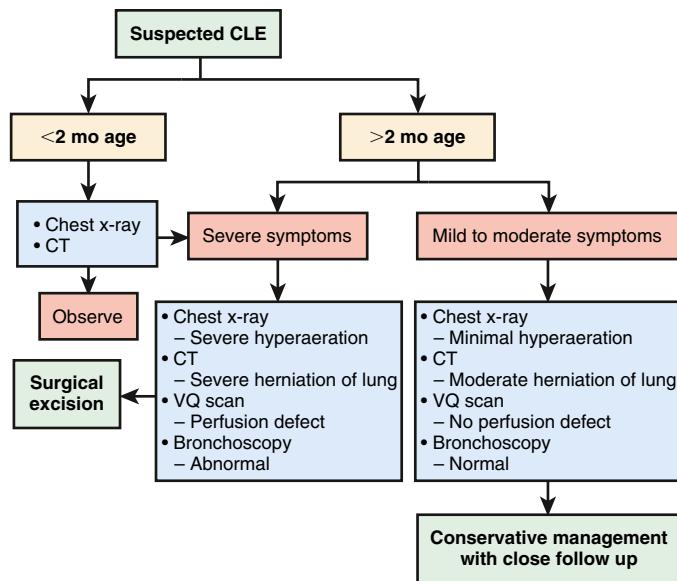


Fig. 441.2 Algorithm for evaluation and treatment of congenital lobar emphysema (CLE). (Adapted from Karnak I, Senocak ME, Ciftci AO, et al. Congenital lobar emphysema: diagnostic and therapeutic considerations. *J Pediatr Surg*. 1999;34:1347–1351, Fig. 4.)

as a *pulmonary artery sling*, can impinge the right main stem bronchus with resultant right-sided hyperinflation or atelectasis producing hyperlucency on either the ipsilateral or contralateral side. **Pulmonary venolobar syndrome** (see Chapter 475), 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.

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 pneumothorax and pneumomediastinum (see Chapters 461 and 462).

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.



Fig. 441.3 Increased transradiancy in the right lower zone. A large emphysematous bulla occupies the lower half of the right lung, and the apical changes are in keeping with previous tuberculosis. (From Padley SPG, Hansell DM. Imaging techniques. In: Albert RK, Spiro SG, Jett JR, eds. Clinical Respiratory Medicine, 3rd ed. Philadelphia: Mosby; 2008: Fig. 1.48.)

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 and in end-stage cystic fibrosis lung disease. Bullous emphysema can also result from inhalational marijuana use. 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. 441.3). The cysts should be differentiated from pulmonary abscesses. In most cases, treatment is not required, as 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

Subcutaneous emphysema results from any process that allows free air to enter into the subcutaneous tissue (Fig. 441.4). The most common causes include pneumothorax or pneumomediastinum (see Chapters 461 and 462). In addition, 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.

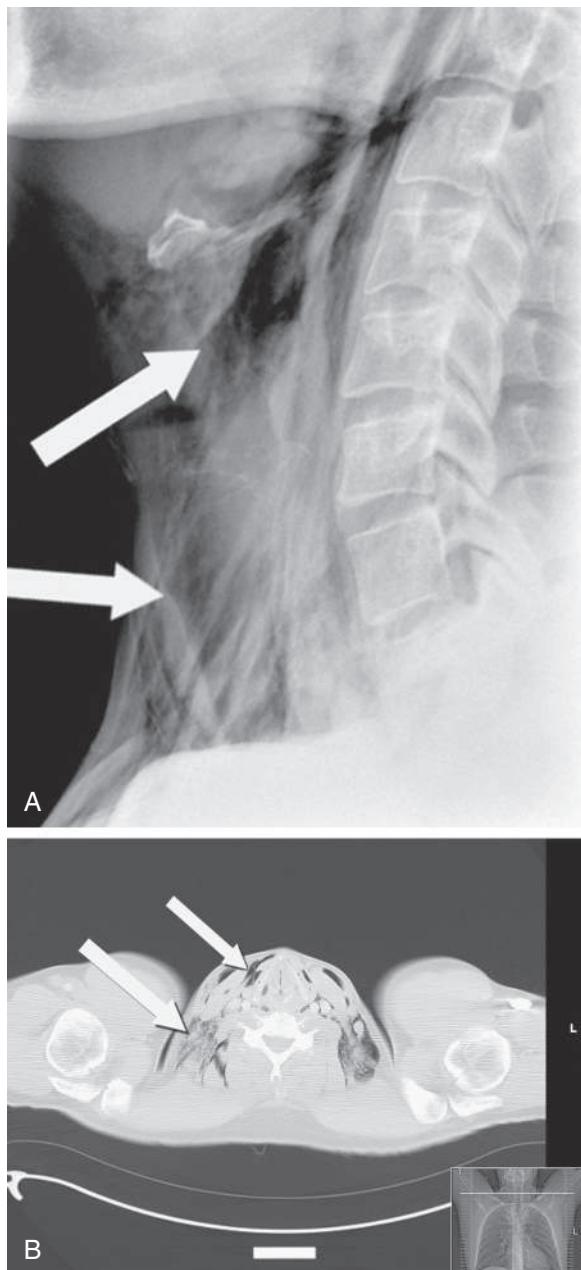


Fig. 441.4 A, Lateral x-ray of neck showing subcutaneous emphysema. B, Axial section CT neck/thorax showing subcutaneous emphysema and pneumomediastinum. (From Zakaria R, Khwaja H. Subcutaneous emphysema in a case of infective sinusitis: a case report. J Med Case Rep. 2010;4:235, Figs. 1 and 2.)

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.

Chapter 442

α_1 -Antitrypsin Deficiency and Emphysema

Vicki K. Masson and Steven R. Boas

Homozygous deficiency of α_1 -antitrypsin (α_1 -AT) rarely produces lung disease in children, but it is an important cause of early-onset severe panacinar pulmonary emphysema in adults in the third and fourth decades of life and a significant cause of liver disease in children (see Chapter 405.5). It is associated with panniculitis and antineutrophil cytoplasmic antibody (cANCA)-associated vasculitis in adults with the PI MZ phenotype.

PATHOGENESIS

The type and concentration of α_1 -AT are inherited as a series of codominant alleles on chromosomal segment 14q31-32.3. (See Chapter 405.5 for a discussion of genotypes and liver disease.) The autosomal recessive deficiency affects 1 in 1,600-5,000 people, but it remains underdiagnosed. Worldwide there are an estimated 116,000,000 carriers and 1,100,000 subjects with severe α_1 -AT deficiency. The normal α_1 -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. Pathogenic variant proteins are not produced (null) or are misfolded (PiZ and others); they can polymerize in the endoplasmic reticulum or be degraded, with subsequent low serum levels. Early adult-onset emphysema associated with α_1 -AT deficiency occurs most commonly with PiZZ (pathogenic variant in SERPINA1 gene), although Pi (null) (null) and, to a lesser extent, other pathogenic Pi types such as SZ have been associated with emphysema.

α_1 -AT and other serum antiproteases help to 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. Polymerized pathogenic proteins in the lungs may also be proinflammatory, and there is evidence of increased oxidative stress. The concentration of proteases (elastase) in an individual's leukocytes may also be an important factor in determining the severity of clinical pulmonary disease with a given level of α_1 -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, which caused inflammation with consequent early disease. Smoking increases the risk of emphysema in patients with mutant Pi types. A newborn screen to identify children with the PiZZ phenotype provides useful guidance in support of smoking cessation for close contacts and reduces adolescent smoking rates.

Physical examination in *childhood* is usually normal. Affected children rarely have growth failure, an increased anteroposterior diameter of the chest with a hyperresonant percussion note, crackles to indicate active infection, or clubbing. Severe emphysema can depress the diaphragm, making the liver and spleen more easily palpable.

LABORATORY FINDINGS

Serum immunoassay measures low levels of α_1 -AT; normal serum levels are ~80-220 mg/dL. Serum electrophoresis reveals the phenotype, and genotype is determined by polymerase chain reaction; whole gene sequencing is possible. In the rare patient with lung disease in adolescence, chest radiograph reveals overinflation with depressed diaphragms. Chest CT can show more hyperexpansion in the lower lung zones, with occasional bronchiectasis; CT densitometry can be a sensitive method to follow changes in lung disease. Lung function testing is usually normal in children, but it can show airflow obstruction and increased lung volumes, particularly in adolescents who smoke.

TREATMENT

Therapy for α_1 -AT deficiency is intravenous replacement (**augmentation**) with enzyme derived from pooled human plasma. A level of 80 mg/dL is protective for emphysema. This target level for augmentation therapy is usually achieved with initial doses of 60 mg/kg IV weekly and results in the appearance of the transfused antiprotease in pulmonary lavage fluid. The Food and Drug Administration has approved the use of purified blood derived human enzyme for ZZ and null-null patients. Replacement therapy is indicated for those with moderately severe obstructive lung disease (forced expiratory volume in 1 second is 30-65% of predicted) or those with mild lung disease experiencing a rapid decline in lung function. Augmentation therapy is not indicated for persons with the PiMZ type who have pulmonary disease, because their disease is not from enzyme deficiency. Recombinant sources of α_1 -AT are under development, but current products are rapidly cleared from the circulation when given intravenously; they may be useful for inhalation therapy. Inhalation of the plasma-derived product is under evaluation. Lung transplantation has been performed for end-stage disease. Multiple strategies for gene therapy are under development.

SUPPORTIVE THERAPY

Standard supportive therapy for chronic lung disease includes aggressive treatment of pulmonary infection, routine use of pneumococcal and influenza vaccines, bronchodilators, and advice about the serious risks of smoking and smoke exposure. Such treatment is also indicated for asymptomatic family members found to have PiZZ or null-null phenotypes but not those with the PiMZ type. The clinical significance of the PiSZ type is unclear, but nonspecific treatment is reasonable. All persons with low levels of serum antiprotease should be warned that the development of emphysema is partially mediated by environmental factors and that cigarette smoking is particularly deleterious. Although early identification of affected persons could help to prevent development of obstructive lung disease, population screening programs are being considered but are currently suspended.

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Chapter 443

Other Distal Airway Diseases

443.1 Bronchiolitis Obliterans

Catherine Kier and Steven R. Boas

Bronchiolitis obliterans (BO) is a histopathologic diagnosis characterized by chronic obstructive lung disease of the bronchioles and smaller airways resulting from an insult to the lower respiratory tract leading to inflammation and fibrosis of the small airways. In the nontransplant patient, BO most commonly occurs in the pediatric population after respiratory infections, particularly adenovirus (see Chapter 309), but also *Mycoplasma pneumoniae* (see Chapter 269), measles (see Chapter 293), *Legionella pneumophila* (see Chapter 254), influenza (see Chapter 305), and pertussis (see Chapter 243); other causes include inflammatory diseases (juvenile idiopathic arthritis, systemic lupus erythematosus [see Chapter 199], scleroderma [see Chapter 201], Stevens-Johnson syndrome [see Chapter 193]) and inhalation of toxic fumes or particulate exposure (NO_2 , incinerator fly ash, NH_3 , diacetyl flavorings from microwave popcorn, papaverine, fiberglass) (Table 443.1). Postinfectious BO (PIBO) may be more common in the Southern Hemisphere. BO is also commonly seen in post lung or bone marrow transplant recipients.

Bronchiolitis obliterans syndrome (BOS) is a clinical diagnosis related to graft deterioration after transplantation, defined as a progressive decline in lung function based on forced expiratory volume in 1 second (FEV_1). The airway obstruction is generally irreversible. BOS is considered once other causes of airway obstruction are excluded. It is recognized as a long-term complication of both lung and bone marrow transplantation, with more than one third of survivors of lung transplantation developing this disorder. Risk factors for the development of BOS include the presence of cytomegalovirus (CMV) pneumonitis, *Aspergillus* colonization, primary graft dysfunction, gastroesophageal reflux, and community-acquired respiratory viruses, as well as prolonged transplantation ischemic time.

PATHOGENESIS

After the initial insult, inflammation affecting terminal bronchioles, respiratory bronchioles, and alveolar ducts can result in the obliteration of the airway lumen (Fig. 443.1). Epithelial damage resulting in abnormal repair is characteristic of BO. Complete or partial obstruction of the airway lumen can result in air trapping or atelectasis. Parenchymal involvement is not seen. **Bronchiolitis obliterans organizing pneumonia (BOOP)**, or what is now termed **cryptogenic organizing pneumonia (COP)**, is a histopathologic diagnosis. Although it is similar to many of the histologic features of BO, COP is also characterized by extension of the inflammatory process from distal alveolar ducts into alveoli with proliferation of fibroblasts (parenchymal involvement).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Cough, fever, cyanosis, dyspnea, chest pain, and respiratory distress followed by initial or no improvement with antibiotics may be the early 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, Swyer-James syndrome (unilateral hyperlucent lung; see Chapter 441) develops. Pulmonary function tests demonstrate variable findings but typically show signs of airway obstruction with a variable degree of bronchodilator response, although more commonly irreversible. 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. 443.2). Table 443.2 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 COP.

TREATMENT

Treatment is a combination of optimal supportive care and anti-inflammatory therapy to impair lymphocyte proliferation. For PIBO, it is recommended that bronchoscopy with bronchoalveolar lavage be performed to rule out persistent viral, bacterial, or fungal pathogens before initiation of systemic antiinflammatory treatment. Corticosteroids should be given early, pulse steroid therapy with methylprednisolone is preferred, and a prolonged course of oral steroids should be avoided to minimize severe side effects and complications or mortality from infections. Immunomodulatory 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 reflux and its association with BO has been raised, with treatment suggested whenever the diagnosis is made. Azithromycin may be effective in patients with BOS. A combination of fluticasone, azithromycin, montelukast, and pulse steroid may halt pulmonary progression of BOS. Potential future treatment options include using mesenchymal stem/stromal cells (MSCs) for immunomodulatory and possibly profibrotic effects and extracorporeal photopheresis (ECP) and total lymphoid irradiation (TLI) for BOS, but additional trials and studies are needed. Patients with asymptomatic or nonprogressive COP 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. BO tends to be severe once progression ensues. In contrast to BO, a better prognosis exists for patients with COP, with complete recovery seen in many patients, although outcome depends on the underlying systemic disease. COP can relapse, especially if treatment duration is <1 year; COP is amenable to repeat courses of oral corticosteroids. Unlike the more common idiopathic COP, progressive COP characterized by acute respiratory distress syndrome is rare but is aggressive in its clinical course, leading to death.

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443.2 Follicular Bronchitis

Catherine Kier and Steven R. Boas

Follicular bronchitis and pediatric lymphocytic interstitial pneumonia are lymphoproliferative lung disorders characterized by the presence of lymphoid follicles alongside the airways (bronchi or bronchioles) and

Table 443.1 Etiology of Bronchiolitis Obliterans

POSTINFECTION

- Adenovirus types 3, 7, and 21
- Influenza
- Parainfluenza
- Measles
- Respiratory syncytial virus
- Varicella
- Mycoplasma pneumoniae*

POSTTRANSPLANTATION

- Chronic rejection of lung or heart/lung transplantation
- Graft versus host disease associated with bone marrow transplantation

CONNECTIVE TISSUE DISEASE/INFLAMMATORY

- Juvenile idiopathic arthritis
- Sjögren syndrome
- Scleroderma
- Systemic lupus erythematosus
- Castleman disease
- Inflammatory bowel disease

TOXIC FUME INHALATION

- NO_2
- NH_3
- Diacetyl flavorings (microwave popcorn)
- Sulfur mustards
- Fly ash (incinerator)
- Fiberglass

CHRONIC HYPERSENSITIVITY PNEUMONITIS

- Avian antigens
- Mold

ASPIRATION

- Stomach contents: gastroesophageal reflux
- Foreign bodies

DRUGS

- Penicillamine
- Cocaine

STEVENS-JOHNSON SYNDROME

- Idiopathic
- Drug induced
- Infection related

From Moonnumakal SP, Fan LL. Bronchiolitis obliterans in children. *Curr Opin Pediatr*. 2008;20:272–278.

infiltration of the walls of bronchi and bronchioles. The disease presents early and is associated with immune dysregulation. Autoantibodies have been found in some children, and in a few patients, disease-causing pathogenic variants have been found in COPA. Most children present with symptoms in the first 2 years of life, but with a lag time of diagnosis to about 4 years. 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 hilar lymphadenopathy, pulmonary nodules, ground-glass opacity, focal consolidation, and bronchiectasis but can also appear normal (see Table 443.2). Definitive diagnosis is made by open lung biopsy (Fig. 443.3). Treatment is limited—systemic steroids, intravenous pulse or oral, showed high response rates. Prognosis is related to early diagnosis and treatment, which are critical to improve the outcome. Some patients have significant progression of pulmonary disease, and others develop only mild obstructive airway disease.

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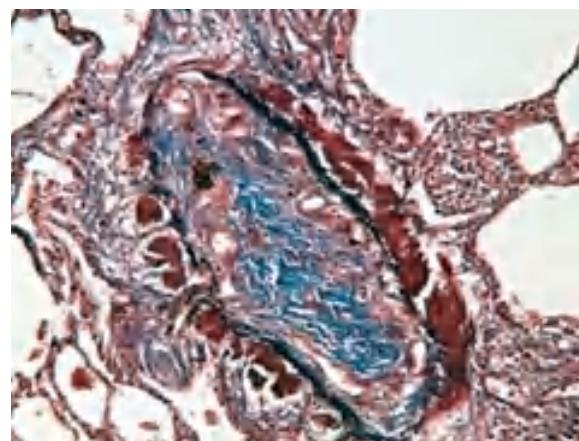


Fig. 443.1 Complete obliteration of airway lumen with fibromyxoid tissue in lung transplant recipient with bronchiolitis obliterans. (From Kurland G, Michelson P. Bronchiolitis obliterans in children. *Pediatr Pulmonol*. 2005;39:193–208.)

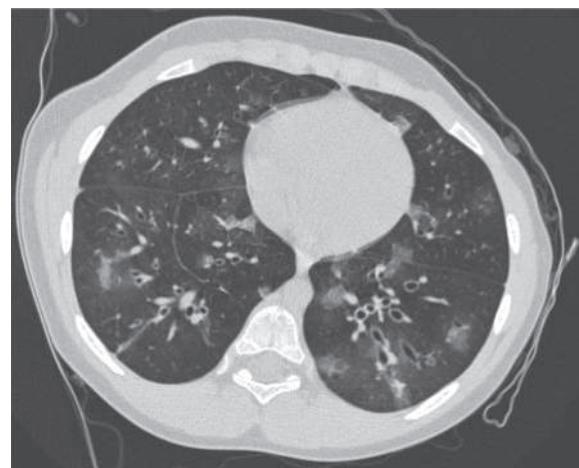


Fig. 443.2 High-resolution CT scan of the chest of a child with bronchiolitis obliterans demonstrating mosaic perfusion and vascular attenuation. Air-trapping is demonstrated by lack of increase in attention or decrease in lung volume in dependent lung. (Image courtesy Alan Brody, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.)

443.3 Pulmonary Alveolar Microlithiasis

Catherine Kier and Steven R. Boas

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. 443.4).

Epidemiology and Etiology

Although the mean age at the time of diagnosis is in the mid-30s, the onset of the disease can occur in childhood and in newborns. PAM is inherited in an autosomal recessive disorder and is caused by a pathogenic variant in the type II sodium phosphate cotransporter NPT2b (*SCL34A2*). To date, there are 27 identified pathogenic variants. This gene is expressed in high levels in the lungs,

Table 443.2 High-Resolution CT Patterns in a Child with Interstitial Lung Disease

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

From Long FR. Interstitial lung disease. In: Slovis T, ed. *Caffey's Pediatric Diagnostic Imaging*, 11th ed. Philadelphia: Mosby; 2008: Table 74.1; original data from Lynch DA, Hay T, Newell JD Jr, et al. Pediatric diffuse lung disease: diagnosis and classification using high-resolution CT. *AJR Am J Roentgenol*. 1999;173:713–718; and Copley SJ, Coren M, Nicholson AG, et al. Diagnostic accuracy of thin-section CT and chest radiography of pediatric interstitial lung disease. *AJR Am J Roentgenol*. 2000;174:549–554.



Fig 443.3 Follicular bronchiolitis in a 3-year-old child with mosaic attenuation and cylindrical bronchiectasis. CT findings suggested bronchiolitis obliterans, 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 T, ed. *Caffey's Pediatric Diagnostic Imaging*, 11th ed. Philadelphia: Mosby; 2008: Fig. 73.71.)

predominantly on the surface of alveolar type II cells. Although the precise role of this protein is unknown, it is speculated that it helps to remove phosphate generated from surfactant metabolism in the alveolar space, as well as functioning as a phosphate regulator 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 and Japan.

CLINICAL MANIFESTATIONS

In early stages of the disease, patients are usually asymptomatic. When symptomatic, patients with PAM usually complain of dyspnea on exertion, nonproductive cough, and fever. 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, gallbladder, sympathetic chain, and testes). Progression to respiratory failure may occur.

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. 443.4). 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 443.2). Diffuse uptake of technetium-99m methylene diphosphonate by nuclear scan has been reported. Bronchoalveolar lavage (BAL) may be helpful. Open lung and transbronchial lung biopsy reveal 0.1- to 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 BAL 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.

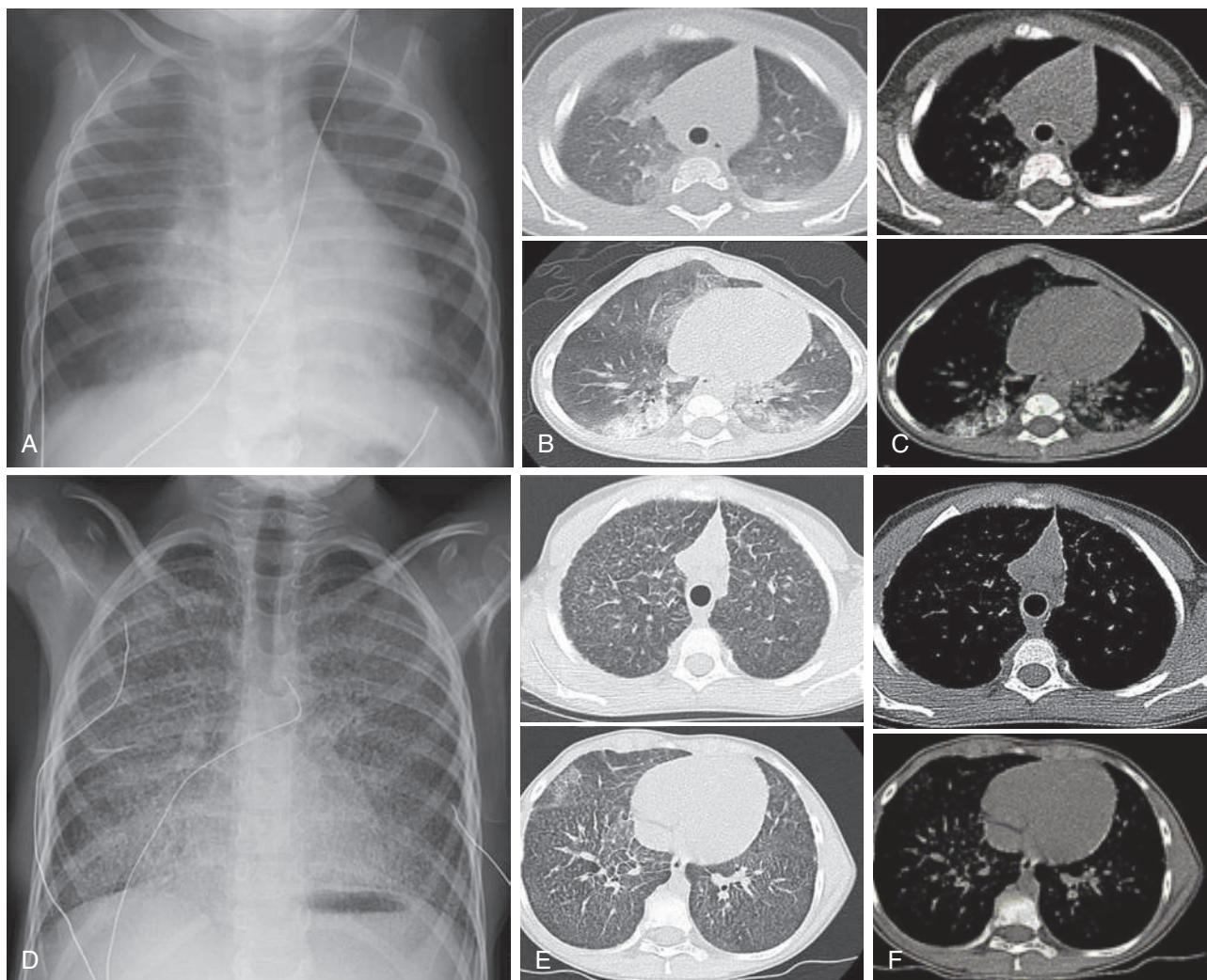


Fig. 443.4 Pulmonary alveolar microlithiasis. Chest radiograph and high-resolution CT performed at the age of 1 year and 8 years. A, Chest radiograph shows bilateral alveolo-interstitial opacities with middle lobe consolidation. Chest CT imaging shows diffuse but patchy ground-glass opacities, alveolar consolidations in the middle and lower lobes, and calcifications in the lower lobes, at parenchymal (B) and mediastinal (C) windows. D, Chest radiograph shows diffuse, even predominant in the lower and middle lobes, dense reticulonodular opacities. Chest CT imaging shows patchy ground-glass opacities, homogenous miliary consolidations with micronodular calcifications and subpleural and interlobular reticulations, parenchymal retractions, and architectural distortion suggestive of fibrosis onset mostly in the upper lobes, at parenchymal (E) and mediastinal (F) windows. (From Sigur E, Roditis L, Labouret G, et al. Pulmonary alveolar microlithiasis in children less than 5 years of age. *J Pediatr.* 2020;217:158–164.e1, Fig. 1.)

The diagnosis can usually be established radiographically. However, lung tissue biopsy, BAL, and detection of a pathogenic variant in the *SCL34A2* gene can also be used to help confirm 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 without recurrence in the transplanted lung.

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.

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Chapter 444

Congenital Disorders of the Lung

444.1 Pulmonary Agenesis and Aplasia

Joshua A. Blatter and Jonathan D. Finder

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 be 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, mucus 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. Referral for management of scoliosis may be necessary.

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444.2 Pulmonary Hypoplasia

Joshua A. Blatter and Jonathan D. Finder

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 124). 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. **Fetal akinesia deformation syndrome** is also associated with pulmonary hypoplasia, in part because of decreased fetal breathing movements.

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 130). 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. Extracorporeal membrane oxygenation can provide gas exchange for a critical period of time and permit survival. Rib-expanding devices (vertically expandable prosthetic titanium ribs and magnetic expansion control rods) can improve the survival of patients with thoracic dystrophies (see Chapter 741).

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444.3 Congenital Pulmonary Airway Malformation (Congenital Cystic Adenomatoid Malformation)

Joshua A. Blatter and Jonathan D. Finder

Congenital pulmonary airway malformation (**CPAM**), formerly known as *cystic adenomatoid malformation*, consists of hamartomatous or dysplastic lung tissue mixed with more normal lung, usually confined to one 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** (echogenic cysts <5 mm). Five histologic and location patterns have been described (Fig. 444.1). **Type 0** (acinar dysplasia) is least common (<2%) and consists of microcystic disease throughout the lungs. The prognosis is poorest for this type, and infants die at birth. **Type 1** (60–70%) 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 one 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** (15–20%) 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, esophageal atresia, skeletal) and carries a poor prognosis. **Type 3** (5–10%) 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 (type 1

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 common; cartilage is rare. The presence of cartilage might indicate a somewhat later embryologic insult, perhaps extending into the 10th to 24th week. 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. 444.2). To better define and differentiate the lesion from other congenital lung malformations, fetal MRI is indicated (Fig. 444.3). Fetal cystic lung abnormalities can include CPAM (40%), pulmonary sequestration (14%) (see Chapter 444.4), or both (26%); the median age at diagnosis is usually 21 weeks of gestation. In one 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, two of whom died in the neonatal period. CPAM volume ratio (CVR)—CPAM volume divided by head circumference—can be used to predict the risk of fetal hydrops. A CVR >1.6 is a high-risk factor for developing hydrops. Lesions causing fetal hydrops have a poor prognosis. Large lesions, by compressing

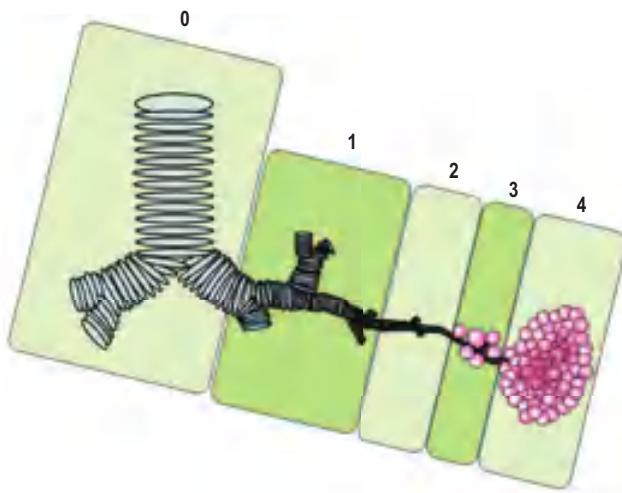


Fig. 444.1 Types of congenital pulmonary airway malformations. Type 0, tracheobronchial; type 1, bronchial; type 2, bronchiolar; type 3, alveolar duct; type 4, distal acinar. (Adapted from Stocker JT. Cystic lung disease in infants and children. *Fetal Pediatr Pathol*. 2009;28:155–184.)

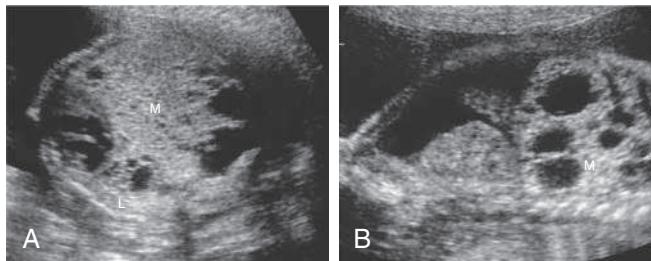


Fig. 444.2 Congenital pulmonary airway malformation (CPAM). A, Massive right CPAM mass (M) with pronounced mediastinal shift is seen. Note the small size of the compressed left lung (L). B, Hydrops fetalis was present; ascites can be seen. C, A shunt was placed in the largest cavity. D, Resolution of the hydrops was seen within 1 week. Cross section through the thorax shows expansion of the ipsilateral and contralateral lungs, repositioning of the heart, and reduction of the mass. (From Obican SG, Odibo A. *Invasive fetal therapy*. In: Lockwood CJ, Copel JA, Dugoff L, et al., eds. *Creasy & Resnik's Maternal-Fetal Medicine*, 9th ed. Philadelphia: Elsevier; 2023: Fig 34-11, p. 633.)

adjacent lung, can produce pulmonary hypoplasia in nonaffected lobes (see Chapter 444.2). 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. MRI 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 131). Neonatal presentations include respiratory distress, cyanosis, tachypnea, or a pneumothorax; hydrops is the most severe presentation. 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 (Fig. 444.4). Occasionally, an air-fluid level suggests a lung abscess (see Chapter 453).

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. Maternal therapy with intravenous betamethasone may inhibit CPAM growth and reverse hydrops. If hydrops persists, a thoracoamniotic shunt may

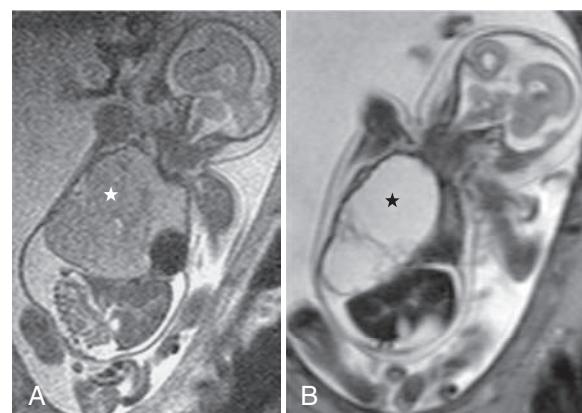


Fig. 444.3 These two fetal MRIs depict a practical prenatal classification for congenital pulmonary airway malformations. A, Microcystic lesion presenting as a solid hyperintense mass (star). B, Macrocytic lesion containing a large cyst >5.0 mm in diameter (star). (From Laje P, Flake AW. *Congenital bronchopulmonary malformations*. In: Holcomb III GW, Murphy JP, St. Peter SD, eds. *Holcomb and Ashcraft's Pediatric Surgery*, 7th ed. Philadelphia: Elsevier; 2020: Fig. 22.3, p. 350.)

be indicated. 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 quite 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 typically recommended to limit malignant potential. If surgery is not performed, the child should have imaging at least yearly to track progression of the lesion. The mortality rate is <10%. Another indication for surgery is to rule out **pleuropulmonary blastoma (PPB)**, a malignancy that can appear radiographically similar to type 1 CPAM or appear concurrently in a type 4 CPAM (mixed lesion). PPB is associated with germline or somatic pathogenic variants in *DICER1*. PPB usually has a systemic feeding vessel and is not connected to the bronchial tree. However, it is often difficult to distinguish a PPB from a CPAM without surgery. In addition to the risk of malignancy, "asymptomatic" patients may have chronic inflammation with subtle systemic manifestations, which parents report resolves after the lesion is resected.

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444.4 Pulmonary Sequestration

Joshua A. Blatter and Jonathan D. Finder

Pulmonary sequestration is a congenital anomaly of lung development that can be intrapulmonary or extrapulmonary, according to the

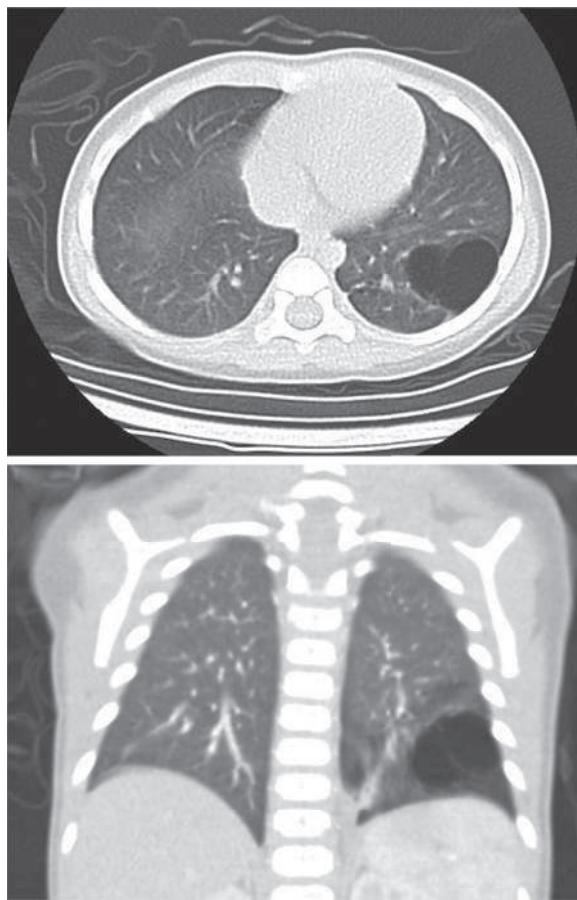


Fig. 444.4 CT scans of CPAM in the left lower lobe of the lung. (From Wong KKY, Flake AW, Tibboel D, et al. Congenital pulmonary airway malformation: advances and controversies. *Lancet Child Adolesc*. 2018;2:290–296, Fig. 1.)

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 (**intrapulmonary**). 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 an 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 444.3), diaphragmatic hernia (see Chapter 131), 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

Recurrent pneumonia in the same lung location is suggestive of a sequestration. 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. 444.5). CT with contrast can demonstrate both the extent of the lesion and its vascular supply. MR angiography is also useful. Ultrasonography can help to 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, hemoptysis 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.

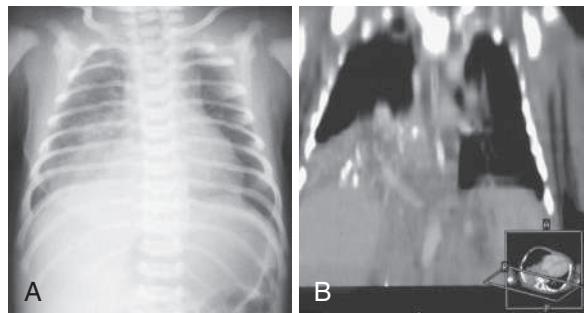


Fig. 444.5 A, Plain chest x-ray showing changes in the region of the right lower/middle lobe of the lung. B, CT showing parenchymal changes in the right lower lobe of the lung in keeping with a sequestration. (From Corbett HJ, Humphrey GME. Pulmonary sequestration. *Paediatr Respir Rev*. 2004;5:59–68.)

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 often recommended for extrapulmonary sequestration as well, but observation can be considered for asymptomatic patients with small lesions. Coil embolization of the feeding artery has also been successful.

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444.5 Bronchogenic Cysts

Joshua A. Blatter and Jonathan D. Finder

Etiology and Pathology

Bronchogenic cysts arise from abnormal budding of the tracheal diverticulum of the foregut before the 16th week 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 infrequent. Diagnosis may be precipitated by enlargement of the cyst, which causes symptoms by pressure on an adjacent airway. When the diagnosis is delayed until an infection occurs, the ciliated epithelium may be lost, and accurate pathologic diagnosis is then impossible. Cysts are rarely demonstrable at birth. Later, some cysts become symptomatic by becoming infected or by enlarging and compromising the function of an adjacent airway.

Clinical Manifestations and Treatment

Fever, chest pain, and productive cough are the most common presenting symptoms. Dysphagia may be present; some bronchogenic cysts are asymptomatic. A chest radiograph reveals the cyst, which can contain an air-fluid level (Fig. 444.6). CT scan or MRI is obtained in most cases to better demonstrate the anatomy and extent of the lesion before surgical resection. Treatment of symptomatic cysts is surgical excision after appropriate antibiotic management. Asymptomatic cysts are generally excised in view of the high rate of infection.

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444.6 Congenital Pulmonary Lymphangiectasia

Joshua A. Blatter and Jonathan D. Finder

Congenital pulmonary lymphangiectasia is characterized by greatly dilated lymphatic ducts throughout the lung. It can occur in three pathologic circumstances: **pulmonary venous obstruction** that produces an elevated transvascular pressure and engorges the pulmonary lymphatics and **generalized lymphangiectasia**, as a generalized disease of several organ systems, including lymphedema, lungs, and the intestines either associated with other syndromes (Noonan, Henneman, yellow nail, trisomy 21) or nonsyndromic. Gorham-Stout disease (vanishing bone disease) presents with pulmonary and abdominal chylous effusions, destructive bone cysts, and multiple lymphangiomas;

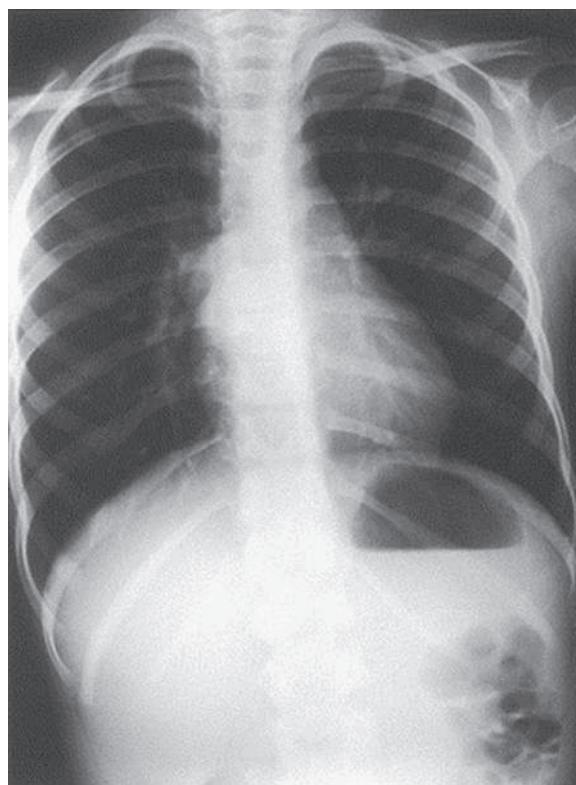


Fig. 444.6 Chest x-ray showing an ovoid, well-defined soft tissue density causing splaying of the carina because of a bronchogenic cyst. (From Williams HJ, Johnson KJ. Imaging of congenital cystic lung lesions. *Paediatr Respir Rev*. 2002;3:120–127.)

primary lymphangiectasia limited to the lung is the third type, which is 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 lymphangiography, lymphoscintigraphy, or lung biopsy (either thoracoscopic or open) (Fig. 444.7).

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. Octreotide, the somatostatin analog, can reduce chylous effusion in some patients. Primary pulmonary lymphangiectasia in the neonate can produce severe pulmonary dysfunction that can require long-term mechanical ventilation; long-term survival and resolution of respiratory insufficiency are possible even in severe cases, especially if the chylous effusions can be managed. Occasionally, the pulmonary venous obstruction is secondary to left-sided cardiac lesions; relief of the latter can produce improvement in pulmonary dysfunction. Sildenafil may reduce pulmonary venous resistance and decrease lymphatic congestion. Sirolimus, which suppresses lymphangiogenesis, may also be beneficial. Lymphangiographic-directed lymphatic injection with ethiodized oil may be another therapeutic option. Generalized lymphangiectasia produces milder pulmonary dysfunction, and survival to mid-childhood and beyond is not unusual.

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444.7 Lung Hernia

Joshua A. Blatter and Jonathan D. Finder

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 454) or asthma (see Chapter 185), 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 three 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

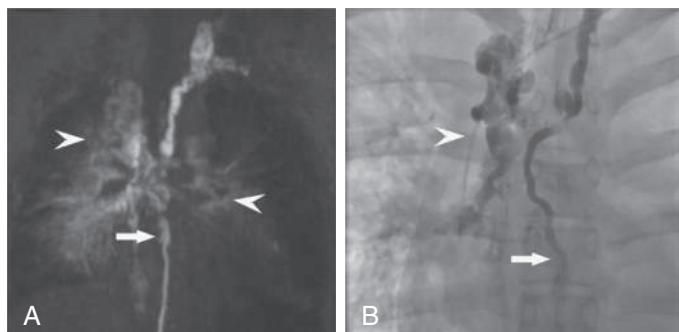


Fig. 444.7 A, Dynamic contrast MR lymphangiogram (DCMRL) in a patient with pulmonary lymphangiectasia demonstrating dilated thoracic duct (TD) (arrow) and abnormal pulmonary lymphatic perfusion in the lung hilum (arrowheads). B, Corresponding fluoroscopy image of the TD of the same patient after injection of contrast material through the microcatheter positioned in the proximal part of the TD, which confirms the dilation of the TD (arrow) and retrograde flow of the contrast in the mediastinal lymphatic ducts (arrowhead). (From Itkin M, McCormack FX. Nonmalignant adult thoracic lymphatic disorders. Clin Chest Med. 2016;37:409–420, Fig. 7.)

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 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.

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444.8 Other Congenital Malformations of the Lung

Joshua A. Blatter and Jonathan D. Finder

CONGENITAL LOBAR EMPHYSEMA AND PULMONARY CYSTS

See Chapter 441.

PULMONARY ARTERIOVENOUS MALFORMATION

See Chapters 481 and 493.

BRONCHOBILIARY FISTULA

A bronchobiliary fistula consists of a fistulous connection between the right middle lobe bronchus and the left hepatic ductal system (Fig. 444.8). Although diagnosis can be delayed until adulthood, this rare anomaly typically manifests with life-threatening bronchopulmonary infections in early infancy. Females 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. Bronchobiliary communications also occur as acquired lesions resulting from hepatic disease complicated by infection.

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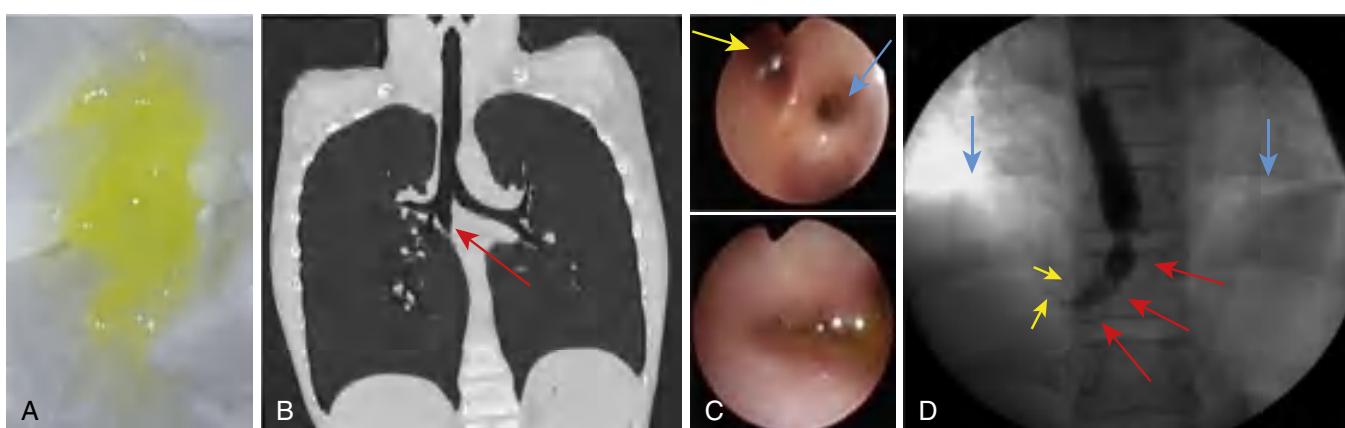


Fig. 444.8 Bronchobiliary fistula. A, Unusually bright yellow, serous sputum was observed. The sputum differed in appearance from the yellow sputum containing leukocytes associated with infections. B, CT scan revealed an abnormal bronchial bifurcation originating in the right main bronchus and extending downward (arrow). C (Top), Bronchoscopic images of the right second carina revealed an anomalous orifice (yellow arrow) in the medial side of the right intermediate bronchus (blue arrow). (Bottom), Close-up photo of the abnormal orifice with yellow, serous secretion. D, Fistulography with a balloon catheter revealed contrast material slowly proceeding through the intraabdominal region (red arrows) to the intrahepatic region (yellow arrows) below the diaphragm (blue arrow). (From Shimizu A, Otani Y, Ishitate M. Congenital bronchobiliary fistula with bright yellow serous sputum. J Pediatr. 2020;243:235–236, Fig. 1.)

Chapter 445

Pulmonary Edema

Brandon T. Woods

Pulmonary edema is an abnormal fluid collection 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 86 and 421).

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 445.1). 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 four 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.
- **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 445.1).

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

Table 445.1 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
Immune reconstitution inflammatory syndrome (IRIS)
Cytokine release syndrome (CRS): CAR-T therapy
Inhaled toxic agents
Circulating toxins
Vasoactive substances such as histamine, leukotrienes, and thromboxanes
Diffuse capillary leak syndrome, as in sepsis, SIRS
Immunologic reactions, such as transfusion reactions
Smoke inhalation
Aspiration pneumonia/pneumonitis
Drowning and near drowning
Radiation pneumonia
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

SIRS, systemic inflammatory response syndrome.

Modified from Robin E, Carroll C, Zelis R. Pulmonary edema. *N Engl J Med*. 1973;288:239, 292; and Deshpande J, Wetzel R, Rogers M. In: Rogers M, ed. *Textbook of Pediatric Intensive Care*, 3rd ed. Baltimore: Williams & Wilkins; 1996:432–442.

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 dilation 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 implicate 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 by 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 87).

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 perivasculär 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 445.2). 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, functional residual capacity, and alveolar ventilation.

Measurement of brain natriuretic peptide, often elevated in heart disease, can help to 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 being to ensure adequate

Table 445.2 Distinguishing Cardiogenic and Noncardiogenic Pulmonary Edema

	HISTORY	EXAMINATION	LABORATORY TESTS	IMAGING
CARDIOGENIC	<ul style="list-style-type: none"> Heart disease Renal disease Uncontrolled HTN Edema Orthopnea Recent administration of IV fluids or blood products 	<ul style="list-style-type: none"> Heart failure examination findings: <ul style="list-style-type: none"> Distended neck veins S3 heart sound Dependent edema Elevated blood pressure Cool extremities 	<ul style="list-style-type: none"> ↑ BNP >1200 pg/mL ↑ Creatinine (in setting of volume overload) ↑ Troponin 	<ul style="list-style-type: none"> CXR: <ul style="list-style-type: none"> CMG pleural effusions Kerley B lines* Bedside USG: homogeneous B lines and sliding pleura in at least two lung regions TEE: <ul style="list-style-type: none"> ↓ LVEF Diastolic filling defect Severe mitral or aortic valvular disease Pericardial effusion with tamponade VSD
NONCARDIOGENIC	<ul style="list-style-type: none"> Sepsis Aspiration event Trauma (long bone fractures) Burn injury Pancreatitis Multiple transfusions 	<ul style="list-style-type: none"> Signs of active infection Extensive burn injury Evidence of trauma (absence of heart failure examination findings) 	<ul style="list-style-type: none"> ↑ WBC BNP <200 pg/mL 	<ul style="list-style-type: none"> CXR: <ul style="list-style-type: none"> Diffuse central and peripheral infiltrates Normal heart size No or minimal pleural effusions Bedside USG: Presence of nonhomogeneous B lines, limited pleural sliding, and other patterns such as subpleural consolidations in at least two to three lung regions TEE: <ul style="list-style-type: none"> Normal LV and valvular function No evidence of volume overload

*Thin 1–2 cm hyperechoic lines indicating thickened interlobular septae in the lung apices or bases.
BNP, brain natriuretic peptide.

Modified from Pannu SR, Christman JW, Crouser ED: Pulmonary edema. In Vincent JL, Moore FA, Bellomo R, Marini JJ (eds). *Textbook of Critical Care*, 8th ed. Philadelphia: Elsevier, 2024. Table 11.1.

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. 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 volutrauma or barotrauma, including pneumothorax, pneumomediastinum, and primary alveolar damage (see Chapter 86.1). 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 hours) 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 87).

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Chapter 446

Acute Aspiration

Anastassios C. Koumourlis

ASPIRATION SYNDROMES

Aspiration of material that is foreign to the lower airway produces a varied clinical spectrum ranging from an asymptomatic condition to acute life-threatening events. Except for cases of self-harm, episodes of acute aspiration are almost always unintentional. Whether the aspiration will lead to the development of symptoms and how severe these will be depends on the amount and nature of the aspirated material.

This chapter focuses on aspiration of **biologic liquids** (e.g., gastric contents) and chemical substances such as hydrocarbons or oils. Other chapters discuss the mechanical obstruction of large- or intermediate-size airways from solid foreign bodies (see Chapter 435), drowning (see Chapter 88), and chronic or recurrent (micro)aspiration (see Chapter 447).

GASTRIC CONTENTS

Aspiration of gastric contents may occur in the context of vomiting in persons who are not able to protect their airways. This can be the result of either a chronic neurologic impairment or temporary suppression of the normal protective reflexes. Such circumstances include drowning, seizures, trauma (especially head injury), and cardiopulmonary resuscitation. The most common nonacute condition that may predispose to aspiration is anesthesia that suppresses the protective airway reflexes (e.g., cough, glottic closure) not only during the procedure but even for hours afterward. Fortunately, because of the strict guidelines of fasting before receiving anesthesia, the actual incidence of aspiration during anesthesia is extremely low (<0.4%). It should be noted that in-office sedation/anesthesia for dental procedures also has the potential to cause suppression of the protective airway reflexes. Other conditions that may lead to vomiting and aspiration are alcohol intoxication and use of illicit drugs such as opiates, both of which can cause severe suppression of the level of consciousness.

The consequences of aspiration of gastric contents vary, depending primarily on the pH and volume of the aspirate and on the amount of particulate material it contains. Increased clinical severity is noted with aspirated volumes greater than 0.8 mL/kg and/or pH <2.5, but significant injury may also occur by fluids with alkaline pH such as bile or even with human breast milk.

Acute aspiration may cause **chemical pneumonitis** that may progress to **acute respiratory distress syndrome (ARDS)** consisting of hypoxemia, hemorrhagic pneumonitis, atelectasis, intravascular fluid shifts, and pulmonary edema. These processes occur rapidly (within minutes to 1–2 hours). There is also 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 later (24–72 hours) and are more prolonged after aspiration of particulate material. Aspiration of gastric contents does not cause infection per se, but it predisposes to infection because of impairment of the airway epithelial defenses. If the patient demonstrates clinical worsening, especially with fever and leukocytosis, secondary bacterial pneumonia should be suspected.

HYDROCARBON ASPIRATION

Hydrocarbons are organic compounds that consist entirely of hydrogen and carbon. They are found in abundance in nature in fossil fuels (crude oil, coal, natural gas) and in plants (and some animals). Hydrocarbons are used in numerous common household or industrial products, thus increasing the possibility of accidental (and/or intentional) exposure. The major types of hydrocarbons and their common uses can be found in Table 446.1.

There are thousands of unintentional exposures to hydrocarbons each year, with the vast majority occurring in children under the age of 5, who drink out of curiosity from poorly secured and unlabeled containers. During adolescence, many exposures are intentional for recreational purposes (e.g., glue sniffing). Among adults a common accidental exposure occurs while attempting to siphon gasoline or among performers such as “fire eaters.” Aspiration of hydrocarbons can occur while drinking the substance or often in the context of vomiting that follows an ingestion. Hydrocarbons have a noxious, unpleasant taste, and they are highly irritating to mucous membranes, thus preventing ingestion and aspiration of large volumes. One exception is the **mineral seal oil** that has a sweet taste that can lead to the ingestion of fairly large amounts.

The toxicity of the hydrocarbons depends on the specific properties of the compound and the amount that was aspirated. The major properties are:

- **Viscosity:** that is the resistance to flow through an orifice. Low viscosity allows *deeper penetration* into the tracheobronchial tree, and it is the property that primarily determines the aspiration potential for hydrocarbons.
- **Surface tension:** that refers to the cohesiveness of molecules along a liquid surface. Low surface tension allows compounds to *spread over a larger area*.

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. 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.

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Table 446.1 Classes and Uses of Common Hydrocarbons (HC)

CLASS AND CHEMICAL COMPOSITION	SOURCES AND EXAMPLES	USES
Aliphatic HC: Straight-chain compounds	Source: crude oil Examples: propane, kerosene, mineral seal oil	Furniture polishes, lamp oil, and lighter fluid
Aromatic HC: Cyclic compounds containing a benzene ring	Source: fossil fuels Examples: benzene, toluene, xylene	Solvents, glues, nail polishes, paints, and paint removers
Halogenated HC: compounds in which at least one hydrogen atom is replaced by a halogen (chlorine, bromine, fluorine)	Source: synthetic Examples: chloroform, bromopropane, carbon tetrachloride, methylene chloride, tetrachloroethylene	Solvents for dry cleaning, solvents for degreasing of metals, adhesives, refrigeration (Freon); insecticides
Terpene HC: cyclic hydrocarbons that consist of 5-carbon building blocks (isoprene)	Source: mostly plants Examples: turpentine, pine oil	Paint thinners (turpentine) and cleaning products (pine oil)

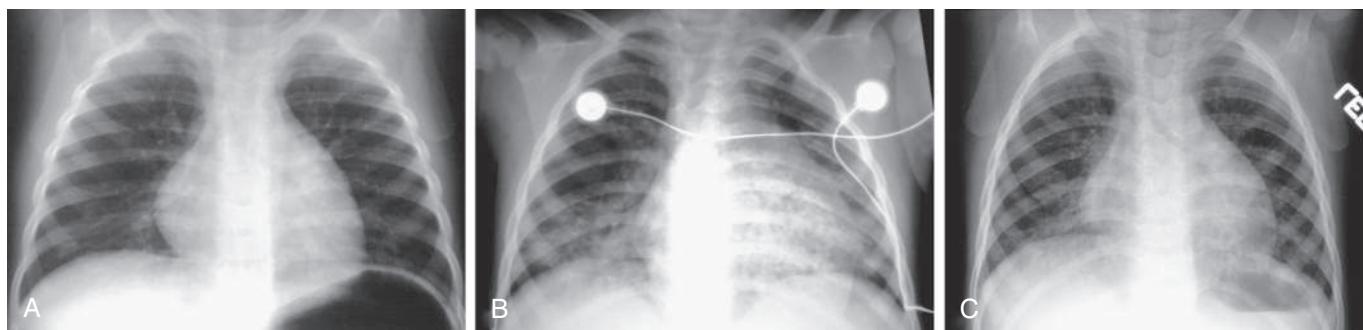


Fig. 446.1 Chest radiographs of a 17-mo-old toddler with hydrocarbon ingestion. A, Three hours after ingestion, the lungs are clear. B, At 24 hours, there are bibasilar coalescing nodular opacities. C, Three days later there is much clearing. (From Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008:1287.)

- **Volatility:** that is the *ability to vaporize*. High volatility increases the risk of pulmonary absorption and central nervous system (CNS) depression.

Hydrocarbons with lower surface tensions (gasoline, turpentine, naphthalene) have more potential for aspiration toxicity than heavier mineral or fuel oils. Ingestion of >30 mL of hydrocarbon, the approximate volume of an adult swallow, is associated with an increased risk of severe pneumonitis.

Most patients with hydrocarbon aspiration tend to remain asymptomatic. When symptomatic, patients have cough, choking, gagging, and vomiting. These usually appear within the first 30 minutes after the aspiration, but they may appear as late as 24 hours. Radiographic findings may present within hours and consist of interstitial or alveolar infiltrates in the perihilar regions and/or in the lower lobes (Fig. 446.1). Additional symptoms develop gradually and may include fever and increased work of breathing. Breath sounds may be decreased (or even absent) with wheezing and/or crackles (especially in the lower lobes). Symptomatic patients (especially those with radiographic abnormalities) require hospitalization for prolonged observation and treatment. Most patients require only supportive therapy (e.g., supplemental oxygen and hydration), and they get discharged within 2–3 days. A small number of patients (~5%) may develop ARDS with severe hypoxemia. Because hydrocarbons evaporate, they displace the alveolar gas, thus exacerbating the hypoxemia that is caused by the development of pulmonary edema and atelectasis that characterize ARDS. Necrotizing pneumonia with pneumatoceles, lipid pneumonia, and hemorrhagic pulmonary edema are typical manifestations of severe cases, and they are often complicated by bacterial superinfection and sepsis, pleural effusions, and air leaks. Fatalities may occur, but most patients are expected to recover. Pneumatoceles can resolve over the course of months.

ASPIRATION OF OTHER SUBSTANCES

Any substance that is not supposed to be found in the airways can cause clinically significant disease. Other substances that can cause

significant lung injury when aspirated or inhaled include baby powder (talc), 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.

One substance that deserves special mentioning is cinnamon, which achieved “notoriety” during the past decade because of the popularity among teenagers and young adults of the so-called “cinnamon-challenge” in which a person attempts to swallow dry cinnamon. Cinnamon is a caustic substance that causes the person to cough violently while it elicits a severe gag that is apparently the “amusing” part of the challenge for the spectators. Despite the gag, the possibility of aspiration is relatively high. Cinnamon causes significant airway inflammation and a potential hypersensitivity reaction that in rare cases may lead to respiratory distress and failure.

PRINCIPLES OF MANAGEMENT

Suctioning of the aspirated material can be effective only if it is performed during or immediately after the aspiration occurs (e.g., vomiting occurring in a patient who is seizing). Once aspiration occurs, the aspirated fluid will be drawn (or pushed) quickly into the distal airways with every spontaneous or positive pressure breath. Thus gastric emptying is generally contraindicated because the vomiting increases the possibility of aspiration. An exception to this rule is the ingestion of a large volume (>30 mL) of certain hydrocarbons with inherent systemic toxicity, especially if the patient exhibits signs of altered mental status. Such compounds include camphor, halogenated carbons, aromatic hydrocarbons, and those containing metals and pesticides (mnemonic: CHAMP). *Gastric emptying should be performed after a cuffed endotracheal tube has been inserted for protection from aspiration.* However, because intubating a patient with a full stomach is a high-risk procedure by itself, it should be performed by a specialist with experience in rapid sequence intubation to prevent vomiting and further aspiration.

Bronchoscopy should be considered if there is suspicion of aspiration of significant particulate material that could be potentially removed (see Chapter 435).

Patients in whom large-volume or toxic aspiration is suspected should be observed for several hours (e.g., 6–8 hours) for signs of respiratory distress and/or hypoxemia. A chest radiograph is warranted. A “negative” chest radiograph taken shortly after the event does not rule out the presence, nor does it predict the severity of aspiration, because the radiographic findings usually lag behind the clinical symptoms (see Fig. 447.1).

If the chest radiograph findings and oxygen saturation are normal and the patient remains asymptomatic after several hours of observation, no other treatment is necessary. The caregivers should be instructed to bring the child back to the hospital if respiratory symptoms or fever develop.

Supplemental oxygen is indicated to treat hypoxemia and/or to decrease the work of breathing. High-flow nasal cannula or noninvasive ventilation such as continuous positive airway pressure or bilevel positive airway pressure should be instituted for patients who develop increased work of breathing, progressive hypoxemia, and/or progressive hypercapnia. If these measures fail to control the symptoms, endotracheal intubation and mechanical ventilation are indicated. In rare cases of refractory respiratory failure, extracorporeal membrane oxygenation may become necessary. Exogenous surfactant has been used with success in some reported cases.

There is no specific pharmacologic therapy for aspiration. Bronchodilators may be tried to prevent and/or reverse the bronchospasm triggered by the aspirate (especially if the patient has a history of airway hyperreactivity/asthma). Use of inhaled and especially of systemic corticosteroids may be reasonable considering that severe aspiration triggers a massive inflammatory response, but their actual benefit is rather inconclusive. Animal studies suggest that to be effective corticosteroids should be given nearly simultaneously with the aspiration event. Prophylactic antibiotics are not generally indicated because aspiration causes a “chemical” and not an infectious pneumonitis. However, the possibility of a secondary infection is high because of organisms (usually anaerobes) from the oropharynx that enter the lower airways with the aspirate and/or organisms that may already colonize the lower airways (e.g., in patients with artificial airways and/or underlying conditions such as bronchiectasis). Thus the decision to start antibiotics prophylactically should be based on the patient’s respiratory status, immune status, and colonization status (if known). Empiric antibiotic therapy is usually targeted against anaerobic organisms. In hospitalized or chronically ill patients (especially those with an artificial airway), coverage of *Pseudomonas*, *Staphylococcus aureus*, and enteric gram-negative organisms should also be considered. If empiric antibiotics are given, they can be discontinued if the condition improves rapidly and the cultures are negative.

PREVENTION

The best prevention of unintentional aspiration is to keep toxic substances out of reach from young children in containers that are clearly labeled and with safety caps. 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. Acid neutralization is not routinely recommended, but it may be considered if the airway epithelium is damaged and thus unable to neutralize the acid. Minimizing use of sedation, monitoring for gastric residuals, and gastric acid suppression may all help prevent aspiration. *Any patient with altered consciousness, especially one who is receiving nasogastric or g-troscopy tube feedings, is at high risk for aspiration.*

PROGNOSIS

Most patients without any underlying conditions usually recover in 2–3 weeks with minimal or no chronic residual clinical symptoms, abnormal radiographic, or lung function changes. Prolonged lung damage may occur, including scarring, bronchiolitis obliterans, and

bronchiectasis. The mortality is relatively low (approximately 5%) and occurs primarily among patients with severe acute or chronic comorbidities. In adults the mortality is much higher (exceeding 20%), but it is difficult to separate the contribution of the aspiration from the effect of the underlying conditions.

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Chapter 447

Chronic Recurrent Aspiration

Anastassios C. Koumbourlis

The air that enters the lungs with every breath travels through the same narrow spaces that solid foods and liquids use to enter the esophagus. That aspiration does not occur routinely is the result of several mechanisms that protect the lower airways. The swallowing mechanism is a complex process that starts early in fetal life but fully matures months after birth; its goal is to receive, process, and transfer the food bolus from the mouth to the esophagus while preventing food particles and/or fluids from entering the trachea. When fully developed, the swallow consists of four phases. The first two (oral preparatory and oral) are voluntary and involve the preparation of the food bolus and its transfer to the back of the throat, whereas the last two (pharyngeal and esophageal) are involuntary. Under normal circumstances, by the time the food bolus reaches the pharynx, the respiration transiently stops, the vocal cords close at the midline, the arytenoid cartilages come close to each other, and the epiglottis flexes toward the posterior wall covering the larynx. This allows the food bolus to slide around the epiglottis into the pyriform sinuses and then into the esophagus where peristalsis and gravity help it move to the stomach. If these four phases are not synchronized (e.g., drinking too fast), aspiration may occur. Oro-pharyngeal incoordination is reportedly the most common underlying problem (with prevalence as high as 48%) associated with recurrent pneumonia in hospitalized children. A wide variety of conditions may impair one or more of the phases of the normal swallow (Table 447.1). Various maxillofacial and oropharyngeal anatomic abnormalities such as micrognathia, macroglossia, and cleft palate affect primarily the first two phases of swallowing, whereas neurologic conditions (affecting the central or the peripheral nervous system and the motor neuron junction) and primary muscle conditions affect the last two. In addition to the mechanisms for airway protection that are part of the normal swallow, there are several reflexes that can prevent aspiration. These include:

- 1. The pharyngeal reflex:** Commonly referred to as the “gag” reflex, it can be elicited by touching the posterior pharyngeal wall, the soft palate, the tonsils, and/or the larynx. The gag reflex causes bilateral acute contraction of the pharyngeal muscles and elevation of the soft palate that prevent the bolus from advancing to the glottis. Damage to the glossopharyngeal and/or vagal nerves affects the reflex unilaterally or bilaterally.
- 2. The laryngeal spasm:** When the glottis and/or subglottis get irritated, they produce acute contraction of the laryngeal muscles that close the vocal cords. This mechanism is very important when liquid and/or particles reach the larynx from below (gastroesophageal reflux [GER] or regurgitation) without involving the normal swallowing mechanism. Despite its protective role, laryngospasm may have negative consequences, especially in infants, who have normally low breathing reserves and can develop hypoxemia and hypercapnia within seconds. In addition, if during laryngospasm the infant attempts to exhale, the

Table 447.1 Conditions Associated with Chronic Aspiration		
DIRECT	IMPAIRED SWALLOWING MECHANISM	PREDISPOSING FACTORS
Anatomic causes <ul style="list-style-type: none"> • Tracheoesophageal fistula • Bronchoesophageal fistula • Laryngotracheal cleft 	Anatomic causes <ul style="list-style-type: none"> • Cleft lip/cleft palate* • Micrognathia • Macroglossia • Scarring (e.g., burns) • Trauma • Facial rigidity (scleroderma, dermatomyositis) 	Anatomic causes <ul style="list-style-type: none"> • Choanal stenosis • Laryngomalacia • Esophageal stricture • Esophageal foreign body • External compression of the esophagus (e.g., vascular ring, mass)
Functional causes <ul style="list-style-type: none"> • Vocal cord paralysis in abduction • Central nervous system disorders suppressing the airway-protective reflexes (severe encephalopathy, coma) 	Functional causes <ul style="list-style-type: none"> • Muscle weakness (neuromuscular disorders) • Bulbar dysfunction (motor neuron disorders) • Nonspecific hypotonia (e.g., trisomy 21) 	Functional causes <ul style="list-style-type: none"> • Gastroesophageal reflux • Esophageal achalasia • Immature swallowing (e.g., prematurity) • Severe tachypnea

*Preoperative and postoperative.

Hering-Breuer reflex may cause apnea (this may be a cause of the GER-related apnea often seen among premature infants).

3. The cough reflex: The presence of material in the glottis and subglottis will normally elicit a cough to expel the “foreign substance.” Thus coughing while eating or drinking is an indication of impaired swallowing and of possible aspiration. However, the absence of cough while eating or drinking does not rule out aspiration because several groups of patients (e.g., premature infants or patients with neuromuscular disorders) may not be able to cough, resulting into the so-called “silent aspiration.”

When anatomic abnormalities connect the respiratory and gastrointestinal tracts, the airway protective mechanisms are completely bypassed, and chronic aspiration ensues. Such abnormalities can be found at the level of the larynx (e.g., laryngotracheoesophageal cleft) or at the proximal tracheobronchial tree (e.g., tracheoesophageal and/or bronchoesophageal fistula).

CLINICAL PRESENTATION

Repeated aspiration of even small quantities of gastric, nasal, or oral contents can lead to chronic airway inflammation presenting as recurrent bronchitis, bronchiolitis, and/or pneumonitis. The symptoms vary, but they usually include chronic unexplained cough (especially during or after feeding), gagging, and wheezing. Noisy (“gurgly”) breathing caused by accumulation of secretions in the hypopharynx is both a predisposing and a predictive factor of aspiration. Infants (especially those born prematurely) may present with apneic episodes associated with laryngospasm. This can happen while drinking, as a result of oropharyngeal incoordination, or in between feedings due to episodes of GER that reaches the laryngeal area eliciting the laryngeal spasm. Fever is not usually a symptom of aspiration, but it may develop at any point because the chronic airway inflammation caused by the aspiration predisposes to secondary infections.

Pathologic Sequelae

Chronic aspiration can lead to irreversible lung damage in the form of bronchiectasis, granulomatous inflammation, fibrosis, and bronchiolitis obliterans. Recurrent episodes of lipid pneumonia have been reported after use of oil-based home/folk remedies popular in several parts of the world that are given orally or nasally to children with impaired swallow.

Predisposing Factors

Many of the anatomic and functional abnormalities listed in Table 447.1 predispose the affected patients to aspiration, although technically they do not cause aspiration by themselves. These include but are not limited to the following:

- **Gastroesophageal reflux** (see Chapter 369): GER is a physiologic mechanism that is present from birth and throughout life. When severe, it predisposes to aspiration by bringing gastric contents near the larynx. However, aspiration will not occur unless the protective airway reflexes are defective. In general, GER is less frequently associated with recurrent pneumonia than is dysphagia. Gastroesophageal reflux disease (GERD; see Chapter 369) can cause pharyngeal and laryngeal edema and vocal cord nodules that may interfere with the swallowing mechanism and lead to aspiration. GERD has been associated with chronic microaspiration and bronchiolitis obliterans in lung transplant recipients.
- **Anatomic and functional abnormalities** such as cleft lip/palate, micrognathia, macroglossia, and laryngomalacia can interfere with the mechanism of bolus formation.
- **Nonspecific hypotonia**, seen in conditions such as trisomy 21 and in otherwise healthy infants (especially those born prematurely), may cause oropharyngeal coordination and lead to recurrent microaspiration.
- **Increased work of breathing**, due to conditions that cause significant nasal obstruction and/or significant tachypnea place otherwise healthy infants at risk for aspiration because they may attempt to breathe and drink at the same time. Thus when a child with an acute respiratory illness who is being fed enterally deteriorates unexpectedly, the possibility of aspiration should be considered.

DIAGNOSIS

A history of unexplained recurrent/persistent respiratory symptoms such as cough and wheezing should always raise suspicions of chronic aspiration. It is then important to determine whether the aspiration occurs from above because of swallowing impairment or from below because of GER. The circumstances around and the timing of the symptoms may offer clues about the exact mechanism. Observation of a feeding is an essential part of the examination when a diagnosis of recurrent aspiration is being considered. Particular attention should be given to nasopharyngeal reflux and difficulty with sucking or swallowing. Symptoms such as choking, cough, stridor, or wheezing occurring during feedings are much more likely the result of impaired swallow. Coughing during or immediately after swallowing points toward anatomic abnormalities (e.g., laryngeal cleft or tracheoesophageal fistula). Symptoms occurring in between feedings, especially in a child with frequent spitting up, vomiting, arching, or complaining of epigastric discomfort, are more likely to be associated with GER.

Voice changes such hoarseness or muffled cry suggest GERD, whereas noisy (wet) breathing suggests pooling of secretions in the hypopharynx. The oral cavity should be inspected for gross abnormalities and

Table 447.2 Diagnostic Modalities for the Detection of Chronic Aspiration

DIAGNOSTIC MODALITY	ADVANTAGES	DISADVANTAGES
Chest radiograph	<ul style="list-style-type: none"> • Easy to obtain and inexpensive • Low radiation exposure 	<ul style="list-style-type: none"> • Findings are not pathognomonic • Does not distinguish between aspiration from above or from below
Computed tomography of the chest	<ul style="list-style-type: none"> • Provides details that may be missed in plain chest x-ray (CXR) 	<ul style="list-style-type: none"> • Findings are not pathognomonic • Does not distinguish between aspiration from above or from below • More expensive • Considerably higher radiation exposure
Esophagogram	<ul style="list-style-type: none"> • Provides information on the anatomy and function of the esophagus (e.g., stricture, hiatal hernia, foreign body, achalasia, decreased motility) • Detects gastroesophageal reflux (GER) • Detects tracheoesophageal fistula and external compression (vascular ring) 	<ul style="list-style-type: none"> • Considerable radiation exposure • Short viewing time • May miss a small H-type tracheoesophageal fistula if the patient is in the supine position
Videofluoroscopic swallowing study (VFSS)	<ul style="list-style-type: none"> • Gold standard for the detection of aspiration even in patients without obvious respiratory symptoms 	<ul style="list-style-type: none"> • Considerable radiation exposure • Requires the presence of a trained speech pathologist • May lead to aspiration of barium that cannot be cleared by the lung
Milk scintiscan	<ul style="list-style-type: none"> • More "physiologic" • Provides significantly longer viewing time • High specificity • No radiation exposure 	<ul style="list-style-type: none"> • Low sensitivity • Does not provide any anatomic details
Salivagram	<ul style="list-style-type: none"> • High sensitivity (similar to VFSS) • No radiation exposure 	<ul style="list-style-type: none"> • Infants may spit out the radionuclide before it is mixed with the saliva and swallowed • Does not provide information about GER
Fiberoptic endoscopic evaluation of swallowing (FEES)	<ul style="list-style-type: none"> • Provides direct observation of the swallowing mechanism • Can be performed at the bedside or in the office 	<ul style="list-style-type: none"> • Moderately invasive • Young patients may "fight" the insertion of the laryngoscope in their nose
"Dye" studies	<ul style="list-style-type: none"> • Simple, easy to perform even at home 	<ul style="list-style-type: none"> • Requires the presence of an artificial airway • Possible toxicity from repeated use
Quantification of lipid-laden macrophages in the bronchoalveolar lavage (BAL) fluid	<ul style="list-style-type: none"> • High sensitivity 	<ul style="list-style-type: none"> • Requires the performance of a bronchoscopy and BAL • Low specificity • Does not distinguish whether the lipids are the result of aspiration or release from cell damage/death

stimulated to assess the gag reflex. Drooling or excessive accumulation of secretions in the mouth suggests dysphagia. Sudden development of crackles or wheezes, especially in the dependent lung segments after feeding, is highly suggestive of aspiration.

The laboratory diagnosis of recurrent microaspiration is challenging because of the lack of pathognomonic tests. Several diagnostic modalities are currently used for the diagnosis of aspiration (Table 447.2) that can be grouped in the following:

- **Radiographs and computed tomography of the chest:** Aspiration may produce the "typical" segmental or lobar infiltrates in the dependent areas of the lung. However, their presence is not pathognomonic, and their absence does not rule out the diagnosis. Thus any abnormal radiographic finding (e.g., diffuse infiltrates, lobar infiltrates, bronchial wall thickening, and bronchiectasis) that cannot be explained by any other process should raise the possibility of chronic aspiration, especially if the patient has any of the aforementioned predisposing factors (Fig. 447.1).
- **Contrast studies:** Various tests, such as esophagogram, modified barium swallow (MBS), and videofluoroscopic swallowing study

(VFSS), are currently considered the "gold standard" for the diagnosis of chronic aspiration. The patient swallows the contrast material (usually barium) under direct fluoroscopic visualization, which provides information on the swallow itself, on the presence of penetration and/or aspiration, and on the anatomy and function of the esophagus.

- **Nuclear scans:** These tests (milk scintigram and salivagram) are based on the oral administration of radionucleotides. Their detection in the lungs is proof of aspiration. A major benefit is that they do not expose the patient to radiation. However, the milk scan has very low sensitivity; the salivagram has much better sensitivity but it does not provide any information on the anatomy or function of the esophagus.
- **Endoscopic studies:** The fiberoptic endoscopic evaluation of swallowing (FEES) allows direct observation of the swallow and documents the aspiration in real time without radiation exposure. However, the child's reaction to placement of the endoscope may alter the assessment of function, depending on the level of comfort and cooperation.

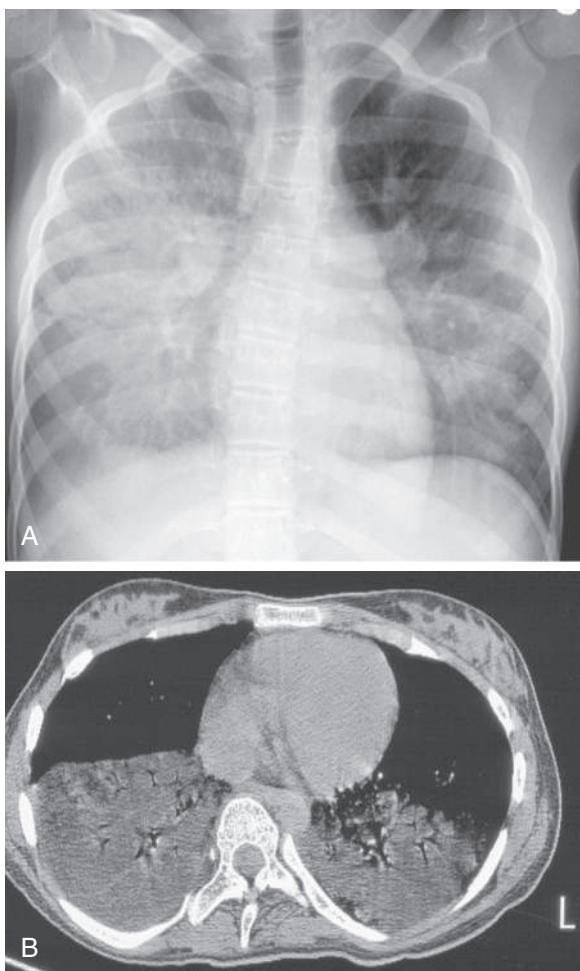


Fig. 447.1 A, Chest radiograph of a developmentally delayed 15-yr-old with chronic aspiration of oral formula. Note posterior (dependent areas) distribution with sparing of heart borders. B, Chest CT scan of same patient. Note lung consolidation in dependent regions is of similar density to subcutaneous fat.

- **Dye studies:** These can be useful tests for patients with artificial airways. A small amount of food coloring (such as methylene blue) is placed in the patient's mouth or into the stomach. If it appears in the tracheobronchial secretions in a few minutes, it confirms aspiration.
- **Analysis of bronchoalveolar lavage (BAL) fluid:** The quantification of lipid-laden alveolar macrophages is a sensitive test for aspiration in children. Its major limitation is that it cannot distinguish between exogenous and endogenous origin of the lipids. The BAF fluid can be also examined for various food substances, including lactose, glucose, food fibers, and milk antigens, as well as pepsin. The specificity and sensitivity of these tests have not been well studied.

MANAGEMENT

There is no specific treatment for aspiration. The focus of its management is the prevention or at least the minimization of the resulting morbidity. The recommended interventions depend largely on the severity of the aspiration and on the nature and prognosis of the underlying condition.

Mild morbidity (e.g., oropharyngeal incoordination due to prematurity):

- **Modifications of the food intake** based on the results of the MBS (e.g., thickening of the liquids, pureed food).

- **Modification of the feeding techniques** (e.g., positioning of the infant in a semierect position, use of special nipples, limiting the amount of food).

These approaches can be used in dysphagia caused by immaturity of the swallowing mechanism (such as that observed in prematurely born and even in term infants) and in impaired swallowing caused by factors that can improve spontaneously (e.g., GER, laryngomalacia) or be corrected surgically (e.g., cleft lip/palate).

Moderate morbidity (e.g., difficulty sucking and swallowing because of chronic lung disease, neuromuscular disorders; presence of tracheostomy):

- **Nasogastric tube feedings:** they can be used temporarily during periods of transient dysphagia. They are minimally invasive but they have several drawbacks such as easy dislodgement and exacerbation of GER (because the lower esophageal sphincter remains open). They can also cause aspiration if placed incorrectly by inexperienced caregivers.
- **Gastrostomy:** should be strongly considered for patients who are not expected to develop or recover the ability to eat by mouth within a relatively short period.
- **Postpyloric feedings:** providing the nutrition into the duodenum or the jejunum is safer because it minimizes (but does not eliminate) GER. Postpyloric feedings can be given either by nasoduodenal or nasojejunal tube or by gastrojejunral (G-J) tube (the latter can be easily threaded through the existing gastrostomy). G-J tubes are recommended for patients with neuromuscular disorders who tend to have significant problems with gastric and intestinal motility.

Severe morbidity:

- **Surgical repair:** Abnormalities such as tracheoesophageal fistula and laryngeal cleft require surgical repair as soon as the infant is stable enough to undergo the operation.
- **Nissen fundoplication** should be reserved for patients whose recurrent aspiration is primarily the result of GER not responding to medical treatment and conservative management. Fundoplication minimizes, but does not eliminate, GER. If tight, it can cause severe retching in patients without muscle weakness.

Management of Oropharyngeal Secretions

The management of nasopharyngeal and oropharyngeal secretions poses a big problem in patients with impaired swallow because the secretions tend to pool in the hypopharynx from where they can easily be aspirated. Saliva can cause inflammation in the tracheobronchial mucosa and introduces organisms from the oropharynx into the lower airways, where they can become pathogenic. The currently available treatments and interventions include the following:

- **Anticholinergic agents:** Medications such as glycopyrrolate and scopolamine are widely used but are of limited effectiveness. When they are given via the gastrostomy tube, they may cause significant dryness in the lower airway, promoting mucus plugging. Nebulization of the intravenous preparation of glycopyrrolate can be effective, but this is not an officially approved use, and the preparation cannot be bought in retail pharmacies.
- **Botox (botulinum toxin type A) injection:** Botox injections in the salivary glands provide a transient decrease in the amount of secretions. To be effective, they need to be repeated every few months under anesthesia.
- **Salivary gland ligation:** This is currently the more definitive intervention for the management of oropharyngeal secretions. Once done, it is irreversible, and therefore it is reserved for very severe cases that are refractory to any other intervention.
- **Tracheostomy:** The role of tracheostomy in the management of chronic aspiration and/or in the management of excessive oropharyngeal secretions is rather controversial. Tracheostomy per se does not prevent aspiration (unless a cuffed tube is used). It actually impairs the swallowing mechanism, and because it is a "foreign body" inside the trachea, it tends to stimulate the production

of more secretions than usual. In addition, it bypasses the natural defenses of the upper airways while it exposes the lower airways directly to the environment, thus increasing the possibility of infection. Its major advantage is that it provides easy access for the suctioning of the lower airways. Most importantly, it provides a secure airway from which positive pressure can be applied, avoiding the risks of emergency endotracheal intubations. It should be considered for patients at high risk for recurrent severe respiratory failure.

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Chapter 448

Immune and Inflammatory Lung Disease

448.1 Hypersensitivity Pneumonia

Michelle L. Hernandez and Stephanie D. Davis

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 inhaled offending antigen 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, and chemicals of low and high molecular weight (Table 448.1). Many of these inciting agents are associated with *occupational diseases*, which occur in locations where children do not regularly work. However, these same diseases can occur in children because of exposures to many similar antigen sources in nonoccupational environments, or in occupational environments with teenage workers. In addition to HP, the same antigens (i.e., antigens from animal proteins and contaminated metal working fluids or other inhaled antigens) may lead to allergic asthma or chronic bronchitis.

More than 300 antigens have been associated with HP. In children, the primary sources have been the result of exposure to **pet birds** (or feathers in bedding and pillows) such as parakeets, canaries, cockatiels, or cockatoos. Aerosol spread of bird droppings can also occur through the vent of a clothes dryer or through heating vents from a garage where the birds were housed. Humidifiers and hot tubs are notorious for contamination with **thermophilic organisms** (bacteria and mold) as well as *Mycobacterium avium* complex. Buildings with inadequate ventilation and insufficient air turnover present an increased risk of mold exposure from prior flooding or damp condensation. Despite exposures to the same antigen sources, members of the same family may exhibit different presentations of allergic disease. For instance, some family members may have symptoms of asthma or rhinitis, whereas another may have HP.

Pathogenesis

The pathogenesis of HP is complex and appears to have a genetic component. Recurrent exposures to environmental agents associated with HP (see Table 448.1) trigger an inflammatory response promoting the development of immune complexes. These immune complexes activate the complement pathway, ultimately resulting in the accumulation of neutrophils in the airway that release enzymes such as neutrophil elastase that damage surrounding lung tissue. Activated macrophages in the lung promote recruitment of lymphocytes into the tissues. Pathology shows alveolitis with a mixed cellular infiltration composed of lymphocytes, macrophage, plasma cells, and neutrophils. Continued exposure to the offending antigen results in the formation of loose, noncaseating granulomas located near the respiratory or terminal bronchioles. Some patients with chronic exposure develop progressive pulmonary fibrosis similar to patients with interstitial pulmonary fibrosis (IPF). Although the mechanisms are not entirely clear, this is thought to occur secondary to recruitment and activation of fibroblasts and uncontrolled production of extracellular matrix cytokines, including transforming growth factor beta (TGF- β). It is critical when a biopsy is being performed (transbronchial or surgical) that the pathologist knows that HP is being considered because there are other **interstitial lung diseases** that produce similar granulomas with subtle location differences depending on their disease origin. Genetic predisposition also appears to be important, primarily in genes involved with antigen processing and presentation (such as major histocompatibility complex [MHC] I and II), lung homeostasis and wound repair, and telomere-related gene mutations.

Clinical Manifestations and Classification

The prevalence of HP is higher among older individuals but can affect children and young adults. It is estimated that HP accounts for 50% of all childhood idiopathic lung diseases (ILDs). HP had been traditionally classified as acute, subacute, or chronic. However, because of the great variability and overlap in the presentation and course of HP, the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax (ATS/JRS/ALAT) guidelines recategorized HP into two phenotypes based on the predominant presence or absence of fibrosis on imaging or histopathologic examination: (1) **nonfibrotic phenotype** and (2) **fibrotic phenotype**.

Regardless of fibrotic or nonfibrotic phenotype, common symptoms include cough and dyspnea after exposure. The time to symptom presentation after exposure can vary from hours to years and may be recurrent in nature. Acute symptoms can be confused with bacterial or viral disease leading to treatment with antibiotics. For example, as early as 4-8 hours after exposure, patients can present with the abrupt onset of cough, chest tightness, dyspnea, fever, chills, body aches, and fatigue (Table 448.2). Rarely, findings of wheezing are present on the initial examination. Rather, tachypnea with fine crackles may be heard by auscultation in the lung bases and presence of mid-inspiratory squeaks. The duration of symptoms has not been definitively associated with the fibrotic or nonfibrotic phenotype.

The long-term prognosis of HP is quite variable, with some patients developing progressive shortness of breath, cough (productive), weight loss, malaise, loss of appetite, hypoxia, and clubbing of the fingers. Those who have been diagnosed with nonfibrotic HP and are able to avoid exposure to the responsible agent may achieve stabilization or full recovery. In contrast, fibrotic HP is associated with reduced survival secondary to respiratory failure, especially among those with a usual interstitial pneumonia (UIP)-like pattern.

Diagnosis

A diagnosis of HP is certain when the known exposure with the associated immune response to the offending antigen is identified, the medical history and physical examination findings are abnormal on examination, and the pattern of the high-resolution computed tomography (HRCT) of the chest and bronchoalveolar lavage (BAL) findings

Table 448.1 Antigen Sources Associated with Specific Causes of Hypersensitivity Pneumonitis

HYPERSensitivity PNEUMONITIS	ANTIGEN SOURCE	HYPERSensitivity PNEUMONITIS	ANTIGEN SOURCE
Bagassosis (mold on pressed sugar cane)	<i>Thermoactinomyces sacchari</i> <i>Thermoactinomyces vulgaris</i>	Maple bark disease (moldy maple bark)	<i>Cryptostroma corticale</i>
Bat lung (bat droppings)	Bat serum protein	Miller's lung (dust-contaminated grain)	<i>Sitophilus granarius</i> (i.e., wheat weevil)
Bible printer's lung	Moldy typesetting water	Moldy hay, grain, silage (farmer's lung)	Thermophilic actinomycetes Fungi (e.g., <i>Aspergillus umbrosus</i>)
Bird fancier's lung (parakeets, budgerigars, pigeons, parrots, cockatiels, geese)	Droppings, feathers, serum proteins	Mollusk shell hypersensitivity pneumonitis	Sea snail shell
Byssinosis ("brown lung") (unclear if a true cause of hypersensitivity pneumonitis; asthma is common)	Cotton mill dust (carding and spinning areas of cotton, flax, and soft hemp)	Mushroom worker's lung	Mushroom spores Thermophilic actinomycetes
Canary fancier's lung	Serum proteins	Paprika slicer's lung (moldy paprika pods)	<i>Mucor stolonifer</i>
Cheese washer's lung (moldy cheese)	<i>Penicillium casei</i> <i>Aspergillus clavatus</i>	Pauli reagent alveolitis	Sodium diazobenzene sulfate
Chemical hypersensitivity pneumonitis	Diphenylmethane diisocyanate (MDI) Toluene diisocyanate (TDI)	Pearl oyster shell pneumonitis	Oyster shells
Coffee worker's lung	Coffee bean dust	Pituitary snuff taker's disease	Dried, powdered cattle or pig pituitary proteins
Composter's lung	<i>T. vulgaris</i> <i>Aspergillus</i> species	Potato riddler's lung (moldy hay around potatoes)	Thermophilic actinomycetes <i>T. vulgaris</i> <i>Faenia rectivirgula</i> <i>Aspergillus spp.</i>
Contaminated basement (sewage) pneumonitis	<i>Cephalosporium</i>	Poultry worker's lung (feather plucker's disease)	Serum proteins (chicken products)
Coptic lung (mummy handler's lung)	Cloth wrappings of mummies	Pyrethrum (pesticide)	Pyrethrum
Detergent worker's lung (washing powder lung)	<i>Bacillus subtilis</i> enzymes	Sauna taker's lung	<i>Aureobasidium</i> spp., other sources
Dry rot lung	<i>Merulius lacrymans</i>	Sequoiosis (moldy wood dust)	<i>Graphium</i> <i>Pullularia</i> <i>Trichoderma</i> spp. <i>Aureobasidium pullulans</i>
Duck fever	Feathers, serum proteins	Suberosis (moldy cork dust)	<i>Thermoactinomyces viridis</i> <i>Penicillium glabrum</i> <i>Aspergillus conidia</i>
Epoxy resin lung	Phthalic anhydride (heated epoxy resin)	Summer-type pneumonitis	<i>Trichosporon cutaneum</i>
Esparto dust (mold in plaster dust)	<i>Aspergillus fumigatus</i> Thermophilic actinomycetes	Tea grower's lung	Tea plants
Feather duvet lung (feather bed, pillow, duvet)	Avian proteins on feathers	Thatched-roof lung (huts in New Guinea)	<i>Saccharomonospora viridis</i> (dead grasses and leaves)
Fish meal worker's lung	Fish meal	Tobacco grower's lung	<i>Aspergillus</i> spp. <i>Scopulariopsis brevicaulis</i>
Furrier's lung (sewing furs; animal fur dust)	Animal pelts	Turkey handling disease	Serum proteins (turkey products)
Grain measurer's lung	Cereal grain (<i>Sporobolomyces</i>) Grain dust (mixture of dust, silica, fungi, insects, and mites)	Unventilated shower	<i>Epicoccum nigrum</i>
Hot tub lung (mists; mold on ceiling and around tub)	<i>Cladosporium</i> spp. <i>Mycobacterium avium</i> complex	Upholstery fabric (nylon filament, cotton/polyester, and latex adhesive)	Aflatoxin-producing fungus, <i>Fusarium</i> spp.
Humidifier fever	<i>Thermoactinomyces</i> (<i>T. vulgaris</i> , <i>T. sacchari</i> , <i>T. candidus</i>) <i>Klebsiella oxytoca</i> <i>Naegleria gruberi</i> <i>Acanthamoeba polyphaga</i> <i>Acanthamoeba castellani</i>	Velvet worker's lung	Unknown (? nylon velvet fiber, tannic acid, potato starch)
Laboratory worker's lung (rats, gerbils)	Urine, serum, pelts, proteins	Vineyard sprayer's lung	Copper sulfate (Bordeaux mixture)
Lifeguard lung	Aerosolized endotoxin from pool-water sprays and fountains	Wine maker's lung (mold on grapes)	<i>Botrytis cinerea</i>
Lycoperdonosis (Lycoperdon puffballs)	Puffball spores	Wood dust pneumonitis (oak, cedar, and mahogany dust, pine and spruce pulp)	<i>Alternaria</i> spp. <i>Bacillus subtilis</i>
Machine operator's lung	<i>Pseudomonas fluorescens</i> Aerosolized metal working fluid	Wood pulp worker's disease (oak and maple trees)	<i>Penicillium</i> spp.
Malt worker's disease (moldy barley)	<i>Aspergillus fumigatus</i> , <i>Aspergillus clavatus</i>	Wood trimmer's disease (contaminated wood trimmings)	<i>Rhizopus</i> spp., <i>Mucor</i> spp.

Table 448.2

Clinical History 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
- Use of hot tub, sauna, swimming pool
- Other family members or workers with similar recurrent symptoms
- Improvement after temporary environment change (e.g., vacation)

are consistent with HP ([Table 448.3](#)). These findings 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. Diagnostic components are reviewed next.

LABORATORY

Most of the abnormal laboratory findings in HP are not specific and represent evidence of activated inflammatory markers or lung injury. For example, nonspecific elevation of immune globulins or the erythrocyte sedimentation rate and C-reactive protein may 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 and have a poor positive predictive value for disease. For example, among asymptomatic pigeon breeders, precipitating antibodies are nearly universal. False negatives can also be seen as a result of fluctuating serum antibody levels over time and a lack of standardized commercial antigens and reagents available for laboratory testing. It is critical that laboratories familiar with the performance of these tests be used. 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 immunoglobulin E (IgE)-mediated disease is not warranted unless there is evidence of mixed lung pathology such as asthma and interstitial lung opacities.

Radiology

Chest radiograph almost always precedes the use of HRCT of the chest in children because of the need for sedation and concerns regarding the risk of being exposed to an increased radiation dose from HRCT. The plain radiograph may 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. 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 this represents the response of the immune system.

HRCT of the chest is important in distinguishing nonfibrotic from fibrotic HP and may reduce the need for a lung biopsy. HRCT of the chest in **nonfibrotic HP** demonstrates (1) at least one abnormality

Table 448.3

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 inciting 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
 - Abnormal response to an inhalation challenge testing to the offending antigen via reexposure to the environment or inhalation challenge to the suspected antigen
2. Clinical, radiographic, or physiologic findings compatible with hypersensitivity pneumonitis:
 - Respiratory and often constitutional signs and symptoms
 - Cough
 - Breathlessness
 - Crackles on auscultation of the chest
 - Weight loss
 - Episodic fever
 - Wheezing
 - Fatigue

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

- High-resolution chest CT findings typical of HP:

- Nonfibrotic HP pattern:
 - At least one HRCT abnormality indicative of parenchymal infiltration (such as ground-glass opacities or mosaic attenuation) in a diffuse distribution
 - At least one HRCT abnormality indicative of small airway disease (such as ill-defined, centrilobular nodules or air trapping) in a diffuse distribution
- Fibrotic HP pattern:
 - Lung fibrosis (irregular linear opacities/coarse reticulation with lung distortion; traction bronchiectasis and honeycombing) in a random or mid-lung zone predominant location
 - At least one abnormality that is indicative of small airway disease
- 3. Bronchoalveolar lavage with lymphocytosis (>20%, often >50%):
- Usually with low CD4:CD8 ratio (i.e., CD8 is higher than normal)
- 4. Histopathology showing compatible changes with nonfibrotic or fibrotic hypersensitivity pneumonitis and the absence of features in any biopsy site to suggest an alternative diagnosis
- Nonfibrotic HP (purely inflammatory):
 - Cellular interstitial pneumonia
 - Chronic cellular bronchiolitis with a lymphocytic peribronchial infiltration
 - Poorly formed nonnecrotizing granulomas located near respiratory or terminal bronchioles
- Fibrotic HP (mixed inflammatory plus fibrotic or purely fibrotic):
 - Chronic fibrosing interstitial pneumonia
 - Airway-centered fibrosis
 - Poorly formed nonnecrotizing granulomas

Data from Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of hypersensitivity pneumonitis in adults. An official ATS/JRS/ALAT clinical practice guideline [published correction appears in Am J Respir Crit Care Med. 2021 Jan 1;203(1):150-151] [published correction appears in Am J Respir Crit Care Med. 2022 Aug 15;206(4):518]. Am J Respir Crit Care Med. 2020;202(3):e36-e69.

revealing evidence of parenchymal infiltration (such as ground-glass opacities or mosaic attenuation) and (2) at least one abnormality revealing evidence of small airway disease (such as ill-defined, centrilobular nodules or air trapping), both distributed in a diffuse pattern. **Fibrotic HP** is characterized by (1) a lung fibrosis (irregular linear opacities/coarse reticulation; traction bronchiectasis and honeycombing) located in a random or mid-lung zone and (2) at least one abnormality that is consistent with small airway disease.

Bronchoalveolar Lavage

BAL is one of the most sensitive tests in supporting the diagnosis of HP. Lymphocytosis frequently exceeding 50% of the recovered cells is seen in the BAL fluid and should alert the clinician to the possibility of HP. Sarcoid, IPF, cryptogenic organizing pneumonia, berylliosis, granite workers lung disease, amiodarone pneumonia, lymphoma, and Langerhans cell histiocytosis may demonstrate lymphocytosis on BAL. All BAL specimens should have flow cytometry measurements of T-cell markers (CD3, CD4, and CD8 at a minimum). The predominant phenotype of the lymphocytosis is CD3⁺/CD8⁺/CD56⁺/CD57⁺/CD10⁻. In the normal circulation, lymphocytes with CD4 markers predominate at a ratio of approximately 2:1 compared with CD8 lymphocytes. *In HP, this ratio becomes approximately equal to or less than 1 (CD4:CD8 ≤1) with either an increase in CD8 lymphocytes or a decline in CD4 lymphocytes.* Although this ratio helps the clinician in making a diagnosis of HP, this BAL finding is not 100% diagnostic for HP. Cryptogenic organizing pneumonia, a rare disease in children, also may present with BAL, where the CD4:CD8 is ≤1, and may be confused initially with HP. This is in sharp contrast to other lymphocytic granulomatous diseases, like sarcoidosis, where the CD4:CD8 is ≥2.

Lung Biopsy

Lung biopsy is necessary to confirm a diagnosis of HP when critical elements are not present, including antigen exposure, a medical history classic for HP, characteristic physical exam findings, chest HRCT findings, and CD8⁺ lymphocytes in the BAL. Open lung biopsy is often the route of choice in young children because of the difficulty in safely obtaining satisfactory amounts of tissue by transbronchial biopsy. Lack of positive serum precipitins to an offending antigen and lack of an exposure history are common reasons for obtaining lung biopsies. It is crucial to inform the pathologist about the suspicion of HP so that the findings can be interpreted appropriately.

Histopathologic examination of **nonfibrotic HP (purely inflammatory)** demonstrates three primary features: (1) cellular interstitial pneumonia, (2) chronic cellular bronchiolitis with a lymphocytic peribronchial infiltration, and (3) nonnecrotizing granulomas near respiratory or terminal bronchioles. **Fibrotic HP (mixed inflammatory plus fibrotic or purely fibrotic)** is histologically characterized by (1) chronic fibrosing interstitial pneumonia, (2) airway-centered fibrosis, and (3) poorly formed nonnecrotizing granulomas. Furthermore, there is an absence of features in any biopsy site to suggest an alternative diagnosis.

Of note, poorly formed noncaseating granulomas and multinucleated giant cells are seen in HP. This is in sharp contrast to the well-formed granulomas seen in sarcoidosis.

Antigen Challenge by Inhalation

Inhalation challenge can support the diagnosis of HP by demonstrating a causal relationship between environmental exposure and symptoms. Inhalation challenge can be performed by two methods: (1) reexposure to the environment where the suspected antigen is present and (2) a 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, performing this challenge is discouraged.

Two abnormal response patterns may be seen. Most commonly, where there is **HP without asthma**, symptoms occur 8-12 hours after direct challenge in the hospital or after reexposure to the source of the antigen. The challenges replicate some or all of the symptoms observed in the acute syndrome with fever, dyspnea, fatigue, and crackles on lung auscultation. Blood drawn before challenge and then repeated during these symptoms often demonstrates an increased neutrophil count compared to baseline. Pulmonary function tests demonstrate a fall in forced vital capacity (FVC) and often a concurrent fall in the

forced expiratory volume at 1 second (FEV₁), with a stable or increasing ratio of FEV₁:FVC reflecting a restrictive defect. Hypoxemia may accompany this decline in pulmonary function along with 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.

Where there is **HP with concomitant allergic asthma**, these patients may experience a biphasic response to the inhalation challenge. These patients may develop an early reduction in FEV₁, followed by a second drop in FEV₁ and FVC 4-6 hours later. The patient may also have accompanying fever and leukocytosis.

TREATMENT

The control of environmental exposure to the offending antigen is key to curing HP and remains the ideal method of treatment and prevention of recurrence. The clinical and pathologic manifestations of nonfibrotic (purely inflammatory) HP are reversible with removal of the offending antigen. Counseling parents and children about the risk of exposure to birds and feathered bedding or other environmental antigens, biologic aerosols, or agricultural dusts that are known to induce HP is important. Certainly, the source of the antigen and type of antigen appear to affect the 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 in which they live.

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

Removal of the 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. Among those with nonfibrotic HP, glucocorticoids at a dose of 0.5 mg/kg/day of prednisone or equivalent (up to a maximum dose of 30 mg prednisone daily) will reduce the immune inflammatory response in the lungs. Comparative trials in adults demonstrate that the use of 4 weeks of therapy is as effective as 12 weeks of therapy. Because of the rapid reversal of symptoms, successful abatement of the environment is sometimes compromised when the family sees improvement before the antigen source removal.

As with nonfibrotic HP, removal of the offending antigen is also recommended for fibrotic HP. However, there is a paucity of clinical trial data outlining the best immunomodulatory strategies for fibrotic HP. Among those patients with fibrotic HP with inflammatory features present, a trial of glucocorticoids may be pursued at a dose of 0.5 mg/kg per day (up to 30 mg per day) for 4-8 weeks, followed by tapering for 3 months. For patients who have not responded to both antigen removal and corticosteroid treatment, azathioprine and mycophenolate mofetil have been used, but their efficacy has not been tested in clinical trials. Case reports have also reported the use of rituximab for HP treatment because of its ability to reduce immune cell complexes. Results have reported mixed clinical efficacy. Antifibrotic drugs that are used for IPF such as nintedanib or pirfenidone are being tested in clinical trials.

448.2 Occupational and Environmental Lung Disease

Michelle L. Hernandez and Stephanie D. Davis

Although occupational and environmental lung diseases include **occupational asthma**, **irritant-induced asthma**, HP, hard metal inhalation lung disease, berylliosis, and air pollution, this chapter focuses on occupational asthma and irritant-induced asthma. Berylliosis has a propensity to form granulomas (see Chapter 448.3). Although some diseases will be seen with regularity, the important role that a 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 often not considered by the clinician.

Occupational asthma *differs* from work-exacerbated asthma. Individuals with occupational asthma develop asthma after exposure to immunologic or nonimmunologic stimuli found in the workplace, whereas those with work-exacerbated asthma already have asthma that worsens in the workplace because of a myriad of exposures.

The vast array of exposures that may cause disease of the lungs is daunting, such as the inhalation of baking flour or household cleaning fluids causing asthma, microwave popcorn that uses diacetyl flavoring resulting in bronchiolitis obliterans, and exposure to thermophilic organisms or mold resulting in HP. The acute eosinophilic pneumonias associated with the 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 presentations among patients 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. Despite similar exposures, some developed HP, others developed asthma, and some displayed no symptoms at all. 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 448.4).

CLASSIFICATION AND PATHOGENESIS

Occupational and environmental lung diseases include numerous syndromes of human lung disease such as **occupational asthma**, **irritant-induced asthma**, reactive upper airway disease syndrome, HP (see Chapter 448.1), air pollution-induced disease, hard metal inhalation lung disease, berylliosis, occupation-induced lung cancer (e.g., mesothelioma from asbestos), and chronic obstructive pulmonary disease. Most of these diseases are not problematic for children, but adolescents may be at risk to develop lung disease through exposure through part- or full-time work or by single exposures, as seen in some types of irritant-induced asthma.

Table 448.4 A Construct (WHACOS) that Has Been Used in Medical Interviewing of Patients, Coworkers, and Family Members when Environmental or Occupational Lung Disease Is Being Considered

W	What do you do?
H	How do you do what you do?
A	Are symptoms Acute or are they Chronic?
C	Do any Coworkers, family, classmates, or friends have the same symptoms?
O	Do you have any hobbies, travel, or animal/pet exposures Outside of school or work?
S	Are you Satisfied with work or school?

Occupational and Environmental Asthma

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 30 minutes to 2 hours 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 hours after the exposure. Treating physicians can take advantage of this physiology by using spirometry before and after work or school or using peak flow measurements hourly during exposure and after leaving the exposure. Because workers and school children have prolonged periods of exposure followed by a number of days without exposure, the use of pulmonary function plus nonspecific bronchial responsiveness (e.g., methacholine) testing is helpful. For example, pulmonary function tests before starting work or school on a Monday of a typical week may be normal. By Friday of this typical work or school week, the baseline pulmonary function indices may have fallen, and nonspecific 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.

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 448.5). 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 agents, including reactive chemicals, transition metals, and wood dusts (Table 448.6). These **low molecular weight agents** are sufficient to induce an immune response, but often *not by an IgE-mediated mechanism*. These low molecular weight chemicals appear to act as haptens that bind directly 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, sex, 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 upon reexposure. If the allergen exposure is sufficient, these proteins can drive the immune response to a T-lymphocyte type 2 phenotype (Th2), even in patients without prior atopic disposition. This occurred in the case of latex allergy, where many nonatopic individuals and patients exposed to allergen in their personal healthcare environment 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 occupational asthma. Unfortunately, despite primary removal of the offending sensitizing agent, symptoms caused by asthma and bronchial hyperresponsiveness continue in roughly 70% of individuals.

Diagnosis of Occupational Asthma

Occupational asthma should be assessed with a full history, physical examination and objective confirmation of an asthma diagnosis using spirometry, and nonspecific bronchial responsiveness. The negative predictive value of methacholine challenge while the patient is still in the workplace is high (98%): a negative methacholine challenge makes the diagnosis of occupational asthma very unlikely in a patient who is continuously exposed to the suspected causative agent. In addition to comparing measures of nonspecific bronchial responsiveness while on and off work, induced sputum and fractional exhaled nitric oxide (FeNO) can increase the diagnostic sensitivity to 94% through identifying the presence of eosinophilic inflammation. Specific IgE testing

Table 448.5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma

OCCUPATION OR ENVIRONMENT	SOURCE	OCCUPATION OR ENVIRONMENT	SOURCE
ANIMAL-DERIVED ANTIGENS			
Agricultural worker	Cow dander	Flight crew	Screw worm fly (<i>Cochliomyia hominivorax</i>)
Bakery	Lactalbumin	Honey processors	Honeybee
Butcher	Cow bone dust, pig, goat dander	Laboratory worker	Cricket, fruit fly, grasshopper (<i>Locusta migratoria</i>), locust
Cook	Raw beef	Mechanic in a rye plant	Confused flour beetle (<i>Tribolium confusum</i>)
Dairy industry	Lactoserum, lactalbumin	Museum curator	Beetles (Coleoptera)
Egg producer	Egg protein	Seed house	Mexican bean weevil (<i>Zabrotes subfasciatus</i>)
Farmer	Deer dander, mink urine	Sericulture	Silkworm, larva of silkworm
Frog catcher	Frog	Sewage plant worker	Sewer fly (<i>Psychoda alternata</i>)
Hairdresser	Sericin	Technician	Arthropods (<i>Chrysopera carnea</i> , <i>Leptinotarsa decemlineata</i> , <i>Ostrinia nubilalis</i> , and <i>Ephestia kuhniella</i>), sheep blowfly (<i>Lucilia cuprina</i>)
Ivory worker	Ivory dust	Wool worker	Dermestidae spp.
Laboratory technician	Bovine serum albumin, laboratory animal, monkey dander	ACARIANS	
Nacre buttons	Nacre dust	Apple grower	Fruit tree red spider mite (<i>Panonychus ulmi</i>)
Pharmacist	Endocrine glands	Citrus farmer	Citrus red mite (<i>Panonychus citri</i>)
Pork producer	Pig gut (vapor from soaking water)	Farmer	Barn mite, two-spotted spider mite (<i>Tetranychus urticae</i>), grain mite
Poultry worker	Chicken	Flour handler	Mites and parasites
Tanner	Casein (cow's milk)	Grain-store worker	Grain mite
Various	Bat guano	Horticulturist	<i>Amblyseius cucumeris</i>
Veterinarian	Goat dander	Poultry worker	Fowl mite
Zookeeper	Birds	Vine grower	McDaniel spider mite (<i>Tetranychus mcdanieli</i>)
CRUSTACEANS, SEAFOOD, FISH			
Canning factory	Octopus	MOLDS	
Diet product	Shark cartilage	Agriculture	<i>Plasmopara viticola</i>
Fish food factory	Gammarus shrimp	Baker	<i>Alternaria</i> , <i>Aspergillus</i> (unspecified)
Fish processor	Clam, shrimp, crab, prawn, salmon, trout, lobster, turbot, various fishes	Beet sugar worker	<i>Aspergillus</i> (unspecified)
Fisherman	Red soft coral, cuttlefish	Coal miner	<i>Rhizopus nigricans</i>
Jewelry polisher	Cuttlefish bone	Coffee maker	<i>Chrysonilia sitophila</i>
Laboratory grinder	Marine sponge	Laborer	Sooty molds (Ascomycetes, deuteromycetes)
Oyster farm	Hoya (oyster farm prawn or sea-squirt)	Logging worker	<i>Chrysonilia sitophila</i>
Restaurant seafood handler	Scallop and shrimp	Plywood factory worker	<i>Neurospora</i>
Scallop plant processor	King scallop and queen scallop	Sausage processing	<i>Penicillium nalgiovense</i>
Technician	Shrimp meal (<i>Artemia salina</i>)	Sawmill worker	<i>Trichoderma koningii</i>
ARTHROPODS			
Agronomist	Bruchus lenthis	Stucco worker	<i>Mucor</i> spp. (contaminating esparto fibers)
Bottling	Ground bug	Technician	<i>Dictyostelium discoideum</i> (mold), <i>Aspergillus niger</i>
Chicken breeder	Herring worm (<i>Anisakis simplex</i>)	MUSHROOMS	
Engineer at electric power plant	Caddis flies (<i>Phryganeidae</i>)	Agriculture	<i>Agaricus bisporus</i> (white mushroom)
Entomologist	Lesser mealworm (<i>Alphitobius diaperinus</i> Panzer), moth, butterfly	Baker	Baker's yeast (<i>Saccharomyces cerevisiae</i>), <i>Boletus edulis</i>
Farmer	Grain pests (<i>Eurygaster</i> and <i>Pyrale</i>)	Greenhouse worker	Sweet pea (<i>Lathyrus odoratus</i>)
Fish bait handler	Insect larvae (<i>Galleria mellonella</i>), mealworm larvae (<i>Tenebrio molitor</i>), green bottle fly larvae (<i>Lucilia caesar</i>), daphnia, fish-feed <i>Echinodorus</i> larva (<i>Echinodorus plasmosus</i>), Chiromids midge (<i>Chironomus thummi thummi</i>)	Hotel manager	<i>Boletus edulis</i>
Fish processing	Herring worm (<i>Anisakis simplex</i>)	Mushroom producer	<i>Pleurotus cornucopiae</i>

Table 448.5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma—cont'd

OCCUPATION OR ENVIRONMENT	SOURCE	OCCUPATION OR ENVIRONMENT	SOURCE
Mushroom soup processor	Mushroom unspecified	Hairdresser	Henna (unspecified)
Office worker	Boletus edulis	Herbal tea processor	Herbal tea, sarsaparilla root, sanyak (<i>Dioscorea batatas</i>), Korean ginseng (<i>Panax ginseng</i>), tea plant dust (<i>Camellia sinensis</i>), chamomile (unspecified)
Seller	<i>Pleurotus ostreatus</i> (spores of white spongy rot)	Herbalist	Licorice roots (<i>Glycyrrhiza spp.</i>), wonji (<i>Polygonatum tenuifolium</i>), herb material
ALGAE		Horticulture	Freesia (Freesia hybrida), paprika (<i>Capsicum annuum</i>), Brazil ginseng (<i>Pfaffia paniculata</i>)
Pharmacist	Chlorella	Laborer	Citrus food handling (<i>dl</i> -limonene, <i>l</i> -citronellol, and dichlorophen)
Thalassotherapist	Algae (species unspecified)	Oil industry	Castor bean, olive oil cake
FLOURS		Pharmaceutical	Rose hip, passion flower (<i>Passiflora alata</i>), cascara sagrada (<i>Rhamnus purshiana</i>)
Animal fodder	Marigold flour (<i>Tagetes erecta</i>)	Powder	Lycopodium powder
Baker	Wheat, rye, soya, and buckwheat flour; Konjac flour; white pea flour (<i>Lathyrus sativus</i>)	Sewer	Kapok
Food processing	White Lupin flour (<i>Lupinus albus</i>)	Sheller	Almond shell dust
POLLENS		Stucco handler	Esparto (<i>Stipa tenacissima</i> and <i>Lygeum spartum</i>)
Florist	Cyclamen, rose	Tobacco manufacturer	Tobacco leaf
Gardener	Canary island date palm (<i>Phoenix canariensis</i>), bell of Ireland (<i>Molucella laevis</i>), bell pepper, chrysanthemum, eggplant (<i>Solanum melongena</i>), <i>Brassica oleracea</i> (cauliflower and broccoli)	PLANT-DERIVED NATURAL PRODUCTS	
Laboratory worker	Sunflower (<i>Helianthus spp.</i>), thale cress (<i>Arabidopsis thaliana</i>)	Baker	Gluten, soybean lecithin
Olive farmers	White mustard (<i>Sinapis alba</i>)	Candy maker	Pectin
Processing worker	<i>Helianthus annuus</i>	Glove manufacturer	Latex
PLANTS		Health professional	Latex
Brewery chemist	Hops	Rose extraction	Rose oil
Brush-makers	Tampico fiber in agave leaves	BIOLOGIC ENZYMES	
Butcher	Aromatic herb	Baker	Fungal amylase, fungal amyloglucosidase and hemicellulase
Chemist	Linseed oilcake, <i>Voacanga africana</i> seed dust	Cheese producer	Various enzymes in rennet production (proteases, pepsine, chymosins)
Cosmetics	Dusts from seeds of sacha inchi (<i>Plukenetia volubilis</i>), chamomile (unspecified)	Detergent industry	Esterase, <i>Bacillus subtilis</i>
Decorator	Cacoon seed (<i>Entage gigas</i>)	Factory worker	<i>Bacillus subtilis</i>
Floral worker	Decorative flower, safflower (<i>Carthamus tinctorius</i>) and yarrow (<i>Achillea millefolium</i>), spathe flower, statice (<i>Limonium tataricum</i>), baby's breath (<i>Gypsophila paniculata</i>), ivy (<i>Hedera helix</i>), flower (various), sea lavender (<i>Limonium sinuatum</i>)	Fruit processor	Pectinase and glucanase
Food industry	Aniseed, fenugreek, peach, garlic dust, asparagus, coffee bean, sesame seed, grain dust, carrot (<i>Daucus carota L.</i>), green bean (<i>Phaseolus multiflorus</i>), lima bean (<i>Phaseolus lunatus</i>), onion, potato, Swiss chard (<i>Beta vulgaris L.</i>), courgette, carob bean, spinach powder, cauliflower, cabbage, chicory, fennel seed, onion seeds (<i>Allium cepa</i> , red onion), rice, saffron (<i>Crocus sativus</i>), spices, grain dust	Hospital personnel	Empynase (pronase B)
Gardener	Copperleaf (<i>Acalypha wilkesiana</i>), grass juice, weeping fig (<i>Ficus benjamina</i>), umbrella tree (<i>Schefflera spp.</i>), amaryllis (<i>Hippeastrum spp.</i>), Madagascar jasmine sap (<i>Stephanotis floribunda</i>), vetch (<i>Vicia sativa</i>)	Laboratory worker	Xylanase, phytase from <i>Aspergillus niger</i>
		Pharmaceutical	Bromelin, flaviastase, lactase, pancreatin, papain, pepsin, serratio peptidase, and lysozyme chloride; egg lysozyme, trypsin
		Plastic	Trypsin
		VEGETABLE GUMS	
		Carpet manufacturing	Guar
		Dental hygienist	Gotu-percha
		Gum importer	Tragacanth
		Hairdresser	Karaya
		Printer	Acacia

Table 448.6	Low Molecular Weight Chemicals Known to Induce Occupational or Environmental Asthma
CHEMICALS	OCCUPATION OR ENVIRONMENT SOURCE
Diisocyanates	
• Diphenylmethane • Hexamethylene • Naphthalene • Toluene	• Polyurethane • Roofing materials • Insulations • Paint
Anhydrides	Manufacturers or users
• Trimellitic • Phthalic	• Paint • Plastics • Epoxy resins
Dyes	Personal or business use of dyes
• Anthraquinone • Carmine • Henna • Persulfate	• Hair dye • Fur dye • Fabric dye
Glue or resin	Plastic
• Methacrylate • Acrylates • Epoxy	• Manufacturers • Healthcare professionals • Orthopedic specialists
Metals	Metal work
• Chromic acid • Potassium dichromate • Nickel sulfate • Vanadium • Platinum salts	• Plating • Welding
Drugs	Exposure to drugs in environment
• β -Lactams • Opioids • Other	• Pharmaceutical workers • Farmers • Healthcare workers
Chemicals	Exposure in the healthcare field
• Formaldehyde • Glutaraldehyde • Ethylene oxide	• Laboratory work • Healthcare professionals
Wood dust	Workers/hobbyists
• Western red cedar (plicatic acid) • Exotic woods • Maple • Oak	• Sawmill • Carpentry • Woodworking

(via percutaneous skin testing or serum IgE) to the causative agent is often impractical given the lack of commercial extracts to the over 300 known causative agents for occupational asthma (see Table 448.5).

Treatment of Occupational Asthma

The management of occupational asthma is centered on exposure reduction and optimized pharmacotherapy with inhaled corticosteroids (ICS) following the National Asthma Education and Prevention Program (NAEPP) and the Global Initiative for Asthma (GINA) guidelines (reviewed in Chapter 185). Ideally, patients would be completely removed from the exposure for the best outcomes. However, in cases where this is not feasible, respiratory protection devices and work accommodations to reduce the exposure should be pursued under the guidance of an occupational hygienist. Because of a lack of commercially available extracts for the causative agent,

allergen-specific immunotherapy has limited applicability for the treatment of occupational asthma for patients who cannot avoid the exposure. For these reasons, omalizumab therapy has been successfully used in small case series to attenuate the IgE response, resulting in reduced exacerbations and systemic and/or inhaled corticosteroid requirements.

Irritant-Induced Asthma and Reactive Airways Disease Syndrome

Irritant-induced asthma is also a form of work-related asthma and has both **acute** and **subacute** phenotypes. As opposed to occupational asthma, irritant-induced asthma results from **nonimmunologic** provocation of bronchial hyperresponsiveness with airflow obstruction.

The most well-characterized presentation of **acute irritant-induced asthma** is **reactive airways dysfunction syndrome** (RADS), where patients present with acute respiratory symptoms within minutes or hours after a single inhalation of an *elevated concentration* of irritant aerosol, gas, or smoke. Many of these exposures are accidental in nature. The clinical manifestations and pathophysiology of RADS have been studied through experimental design or epidemiology studies involving exposure to chlorine gas, acetic acid, dimethylaminoethanol, chlorofluorocarbons, epichlorohydrin, and diisocyanates. Patients with RADS typically can pinpoint the exact time of onset of symptoms and the exact number of hours post exposure. 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**.

Predisposing factors for the development of RADS are not well characterized. 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 before this catastrophe did not increase the risk for an individual to develop RADS.

The pathogenesis of RADS follows a typical pattern, driven by the initial injury to the airway epithelium. Initial histology demonstrates rapid mucosal denudation accompanied by a submucosal fibrinous, hemorrhagic exudate. Subepithelial edema subsequently occurs with epithelial layer regeneration, basal and parabasal cells increase, and eventually areas of fibrosis form. The desquamation, fibrosis, basement membrane thickening, and basal cell regeneration are more characteristic of RADS than occupational asthma. This may explain the limited response to bronchodilator therapy in this syndrome compared to asthma.

In contrast to the acute onset of symptoms after exposure seen with RADS, individuals with **subacute irritant-induced asthma** present with a more insidious onset of symptoms. Because of the recurrent nature of the low concentration of the chemical exposure, patients may initially not be able to identify the underlying trigger. **Subacute irritant-induced asthma** has been described through epidemiologic studies and characterized by (1) the insidious onset of symptoms occurring after *multiple high exposures to irritants* (such as what occurred among some rescue workers at the World Trade Center) or (2) single or multiple exposures to irritant chemicals in *low concentrations*. 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.

Table 448.7**Criteria for Reactive Airways Disease (Dysfunction) Syndrome**

- Documented absence of preceding respiratory symptoms
- Onset after single specific high-level exposure incident
- Exposure to very high concentration of gas, smoke, fumes, or vapors with *irritant* properties
- Onset of symptoms within 24 hours after exposure with persistence for ≥3 months
- Symptoms similar to asthma with cough, wheeze, and dyspnea
- Presence of airflow obstruction on pulmonary function ± nonspecific bronchial (methacholine) hyper-responsiveness
- Other pulmonary disease excluded

Data from Varney VA, Evans J, Bansal. Successful treatment of reactive airways dysfunction syndrome by high-dose vitamin D. *J Asthma Allergy*. 2011;4:87–91.

Diagnosis of Irritant-Induced Asthma

Initial evaluation of the patient with acute (RADS) or subacute 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. In patients with both acute and subacute irritant-induced asthma, the chest radiograph is frequently normal or may reveal hyperinflation. Ideally, if the patient is not in significant distress, complete pulmonary function testing with spirometry, assessment of bronchodilator reversibility, and nonspecific bronchial provocation with methacholine are helpful in the initial evaluation.

Table 448.7 lists the criteria for a diagnosis of RADS. Asthma-like symptoms and airway hyperresponsiveness occur and often persist for prolonged periods. Unlike typical asthma, *RADS is often not reversible after administration of a bronchodilator*. This is probably a consequence of the direct injury to the epithelium and subsequent submucosal fibrosis.

Treatment of RADS and Irritant-Induced Asthma

Treatment of acute (RADS) and subacute irritant-induced asthma focuses on prevention of exposure. Because the exposure in RADS is often associated with a single known exposure, this task is readily accomplished. The low, persistent exposures associated with subacute irritant-induced asthma are more challenging to identify and remove.

Implementing treatment guidelines for asthma is recommended when intervention is required beyond antigen removal. Managing an acute presentation of RADS is exactly the same as managing an acute asthma exacerbation. Short-acting β-agonist treatment may not be effective; a trial of inhaled ipratropium may add benefit in the short term. For moderate to severe symptoms and FEV₁ values that are less than 70% of predicted, administration of systemic glucocorticoids (2 mg/kg prednisone equivalent, up to 60 mg daily) can be beneficial based on some clinical case studies and animal studies. Unlike the typical 5-day courses of systemic glucocorticoids for asthma exacerbations, many patients remain symptomatic beyond 5 days as a result of the extent of the airway epithelial injury. Steroid treatment may be prolonged up to 10–15 days after the onset of symptoms; a slow taper of corticosteroids may be implemented after the 10–15 days. High-dose ICS therapy with or without long-acting β-agonists may be added while the systemic steroids are being tapered. The initial high-dose ICS regimens are based on the NAEPP and the GINA guidelines. For patients whose initial symptoms are not as severe and/or spirometry demonstrates milder airway obstruction (FEV₁ greater than or equal to 70% of predicted), high-dose ICS therapy alone can be started without requiring systemic corticosteroid treatment. Once patients' asthma symptoms are improved, ICS doses can be tapered by increments of 25–50% over a period of up to 6 months in some case series based on patient symptoms. However, prolonged ICS treatment beyond 6 months has also been noted.

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448.3 Granulomatous Lung Disease

Timothy J. Vece, Eveline Y. Wu, and Stephanie D. Davis

GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis (GPA), formerly *Wegener granulomatosis*, is a disease that involves both the lower and upper respiratory tracts with granulomatous inflammation of small- to medium-sized vessels (see Chapter 210). Pulmonary disease is frequently associated with glomerulonephritis. The simultaneous presence of pulmonary and renal disease should immediately raise the suspicion for GPA, microscopic polyangiitis, or anti-glomerular basement membrane (anti-GBM) disease (see Chapter 448.5).

Epidemiology

The prevalence of GPA during childhood is rare, but epidemiologic data suggest an increase in cases in the last 2 decades. The median age at diagnosis is 10–14 years, and there is a female predominance of 3:4:1. Improved clinical recognition, disease classification, and tests, such as antineutrophil cytoplasmic antibodies (ANCAs), have helped in the diagnosis of this rare disorder.

Etiology and Pathogenesis

In GPA, the development of both upper and lower airway disease with granulomas implies that exposure to antigens in the airways of an endogenous or exogenous source is involved with aberrant innate and adaptive immune responses. Neutrophils are a key effector cell. There is also 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 1 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 and type 17 cytokines (interleukin [IL]-17, TNF, and IFN-γ). Such an inflammatory response may be sufficient to induce and sustain granuloma formation.

ANCAs are autoantibodies reactive against proteins in the cytoplasmic granules of neutrophils and monocytes and are found in 90% of patients with GPA. The most common ANCAs in GPA have a cytoplasmic fluorescence pattern (c-ANCA) and usually indicate antibodies against proteinase-3 (PR3-ANCA). Perinuclear fluorescence (p-ANCA) usually indicate antibodies directed toward myeloperoxidase (MPO-ANCA), which are less common in GPA. Approximately 5–10% of children 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 symptoms. 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 this is more common in adults. Sinusitis may be present, and pulmonary disease occurs in the majority of patients. Symptoms range from cough, hemoptysis (seen in less than 50% of pediatric patients), 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 *pulmonary capillaritis*, the other main component seen on histology, can be seen in other disorders, including anti-GBM disease, microscopic polyangiitis, idiopathic pulmonary capillaritis, and IgA vasculitis (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 and granulomas on lung biopsy along 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 patients.

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

Laboratory and Pathology

PR3-ANCA are found in 70–90% of children with GPA, and in the correct clinical situation are sufficient for the diagnosis of ANCA-associated vasculitis, although it may be difficult to differentiate GPA from MPA. In unusual or uncertain cases, tissue diagnosis is required. In lung tissue, the usual pathology demonstrates multiple parenchymal nodules that may be located in either the bronchial, vascular, or interstitial tissues (Fig. 448.1). The granulomatous inflammation is often found in areas of necrosis and/or vasculitis.

Renal biopsy rarely demonstrates granulomas or vasculitis. Rather, kidney tissues may show focal, segmental, or necrotizing glomerulonephritis without deposits of immune complexes. Kidney biopsy is preferred when a histopathologic diagnosis is required, as kidney biopsy has a lower morbidity and mortality than lung biopsy. 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 imaging findings are quite variable in GPA. Chest radiography may reveal multiple infiltrates, nodules, cavitary lesions, or ILD. Fleeting infiltrates may be seen when recurrent hemorrhage is a clinical manifestation. HRCT of the chest often demonstrates more extensive lung disease and the cavitation associated with the necrotizing nature of the disease (Fig. 448.2).

Treatment

Rapidly progressive, debilitating disease may occur if there is a failure to diagnose GPA. One early series of patients reported that death occurred in 90% of patients within 2 years of diagnosis. Glucocorticoid therapy alone resulted in relapses and inadequate control of disease in many subjects.

Therapy is divided into *induction* and *maintenance* phases. Systemic corticosteroids, while ineffective as monotherapy, are a mainstay of therapy in conjunction with other immune-suppressive agents. Prednisone can be given orally. Alternatively, intravenous methylprednisolone may be used at a dosage of 10–30 mg/kg (max 1 g) administered weekly or for 3 consecutive days monthly. Combination therapy traditionally includes cyclophosphamide given either orally at 2 mg/kg/day or intravenous dosing at 15 mg/kg monthly. Rituximab, an anti-CD20 antibody, is as effective as cyclophosphamide in inducing remission of GPA. Rituximab dosing is either 350 mg/m² given weekly for the first 4 weeks or 750 mg/m² given on initiation of therapy and 2 weeks after initiation. A second dose of 500 mg/m² is often given 6 months after the first course of rituximab. Induction therapy should be continued for 3–6 months.

Continued therapy is required past the initial induction phase to maintain remission. Because of the toxicity of cyclophosphamide, other immune-suppressive agents are preferred. Methotrexate and azathioprine have been shown to be noninferior to cyclophosphamide in maintaining remission, whereas mycophenolate mofetil has higher relapse rates than azathioprine. Rituximab is also used for maintenance remission and is associated with lower risk of major relapse compared with azathioprine, particularly for patients with GPA and PR3-ANCA. Systemic steroid dosages should be progressively weaned at the beginning of the maintenance phase of therapy to a dosage of 5–10 mg/day. Maintenance therapy should be continued for an additional 1.5–2 years.

Adjuvant therapy with plasma exchange may be considered when life-threatening GPA disease presents. This is advocated on the premise that ANCAs are inducing disease and will be removed from the

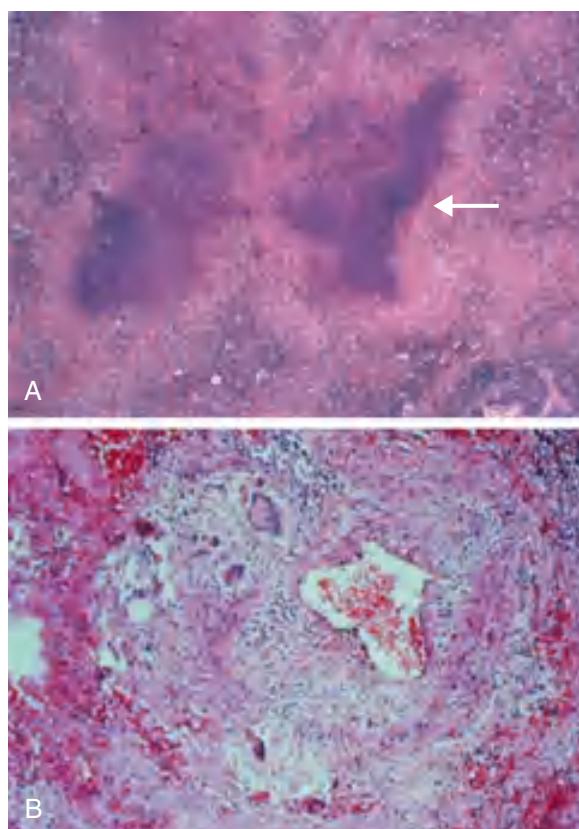


Fig. 448.1 A, Low-power view of granulomatous inflammation and geographic necrosis (arrow) in a lung biopsy from a patient with GPA. B, Granulomatous vasculitis involving a small pulmonary artery in the lung of a patient with GPA. The vessel wall is markedly thickened with an inflammatory infiltrate that includes multinucleated giant cells. (From Sneller MC, Fontana JR, Shelhamer JH. *Immunologic nonasthmatic diseases of the lung*. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. *Middleton's Allergy Principles and Practice*, 8th ed. Philadelphia: Elsevier; 2014: Fig. 62.1B and C.)



Fig. 448.2 Chest CT scan of a patient with granulomatosis with polyangiitis shows typical nodular lung infiltrate with cavitation. (From Sneller MC, Fontana JR, Shelhamer JH. *Immunologic nonasthmatic diseases of the lung*. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. *Middleton's Allergy Principles and Practice*, 8th ed. Philadelphia: Elsevier; 2014: Fig. 62.1A.)

circulation with this intervention; its use has been favorably evaluated in GPA-induced renal disease. 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 nine trials suggest that adjuvant plasma exchange may be associated with improved renal outcome. Other adjuvant therapy includes high-dose intravenous immunoglobulin (IVIG) in recalcitrant disease, which acts to cross-link IgG and likely decrease circulating ANCA antibodies.

Recurrent disease remains a major problem, with relapse rates of up to 50% reported in most studies. ANCA levels do not always correlate with disease activity or severity. Patients with isolated disease of the sinuses and nose may not require such toxic therapy. Therapy with topical corticosteroid and antibiotics for infection appear to be warranted. If unsuccessful, steroids with methotrexate appear to be an effective therapy.

The development of subglottic stenosis requires specific treatment. Use of cyclophosphamide with oral corticosteroid may only partially treat the airway disease or not treat the airway disease at all. Local injection of a prolonged-acting corticosteroid may 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 multisystem inflammatory disease with a characteristic histology of *noncaseating granulomas* (see Chapter 209). It has been postulated that sarcoidosis represents an exaggerated immune response to a yet-to-be-identified agent from the environment that is likely inhaled in a susceptible host. Sarcoidosis remains a diagnosis of exclusion from other diseases, with granuloma formation noted on histology, such as chronic granulomatous disease (CGD), granulomatous lymphocytic interstitial lung disease (GLILD) associated with common variable immune deficiency (CVID), HP associated with some drugs and inhalation agents, GPA, typical and atypical *Mycobacterium*, *Pneumocystis jiroveci*, and malignancy.

Epidemiology and Pathogenesis

The Black population is disproportionately affected by sarcoidosis; however, it can present in any group. Because an asymptomatic sarcoid-like distribution of noncaseating granulomas may be found at autopsy, the contribution of the granulomas to the disease is not clear. In countries that perform chest radiograph screening, up to 50% of people diagnosed with sarcoidosis are asymptomatic. The mortality and severity of sarcoidosis are poorer among Black patients; this is likely multifactorial, with racism and healthcare inequities playing a significant role. Sarcoidosis is more endemic in the Southeastern and South Central United States. There have been clusters of disease in families, and genetic testing suggests that the MHC linkage on the short arm of chromosome 6 is most likely to be observed.

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, the transfer of disease by organ transplant, and the reproducible noncaseating granuloma formation only noted in patients with sarcoidosis in the skin when homogenized lymph node tissue from patients with sarcoid is injected intradermally (Kveim-Siltzbach test) have supported this hypothesis.

Clinical Manifestations

Sarcoidosis is rarely found in young children. Skin rash, uveitis, and arthritis are seen most often in younger children without pulmonary symptoms. In older children, the presentation is similar to adults, with multisystem disease being the most common. 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 can be less progressive compared with adults, and patients can 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.

Patients may present with malaise, fever, and weight loss. Those with lung disease are more likely to be asymptomatic as the presentation. When symptomatic, patients demonstrate shortness of breath, cough,

and dyspnea. Younger children are more likely to manifest the disease as iridocyclitis, skin rash, and arthritis. Black 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 in the pleural fluid. Unusual but reported findings include cases of pneumothorax, hemothorax, and chylothorax. One specific syndrome, **Lofgren syndrome**, with hilar lymphadenopathy, erythema nodosum, and migratory polyarthralgias, is almost exclusively seen in females. 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 40% of adults with stage 1 disease have endobronchial involvement found at bronchoscopy. The higher the staging level of the disease, the more likely patients are to have airway involvement.

Diagnostic Laboratory Testing

The most common but nonspecific findings are hypergammaglobulinemia, elevated acute-phase reactants, hypercalcemia, 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 sarcoidosis. False-positive tests occur from other diseases, so it is not considered a diagnostic test but may be used for monitoring disease activity.

Pulmonary function tests can be performed accurately in most children older than the age of 4 years. There are no specific diagnostic findings of spirometry, lung volumes, or diffusion capacity in sarcoidosis. Restrictive lung disease has been reported, but obstruction may be present because of an airway granuloma or lymph node compression. A decline in diffusion capacity when alveolitis is present in hypersensitivity pneumonitis could help diagnostically when attempting to differentiate sarcoidosis from HP before biopsy.

BAL is of great help when differentiating other diseases from sarcoidosis. BAL in sarcoidosis shows a marked predominance of CD4⁺ T cells. A lymphocyte percentage >16% on BAL, a CD4:CD8 ratio >4:1, and noncaseating granulomas on bronchial biopsy in the presence of abnormal angiotensin-converting enzyme levels are nearly completely diagnostic for sarcoidosis. In addition, T cells are activated on BAL in sarcoidosis. BAL in HP shows a significant change in the balance of CD4⁺ to CD8⁺ T cells, with the two cell types being nearly equal compared with the normal mild predominance of CD4⁺ T 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 with no detectable D-dimers in unaffected controls.

Histopathology

The characteristic feature of sarcoidosis is the noncaseating granuloma formation in the lung (Fig. 448.3). 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 an accumulation of inflammatory cells, including monocytes, macrophages, and lymphocytes, that accompanies the granulomas. Multinucleated giant cells are frequently found among the epithelioid cells within the granuloma follicle. These may show cytoplasmic inclusions (e.g., asteroid bodies and Schaumann bodies) and some birefringent crystalline particles made of calcium oxalate and other calcium salts. These are most often identified in the upper lobes of the lungs, which may lead to confusion with diseases such as HP, eosinophilic granuloma, collagen vascular disease, pneumoconiosis, and infectious disease such as tuberculosis or histoplasmosis.

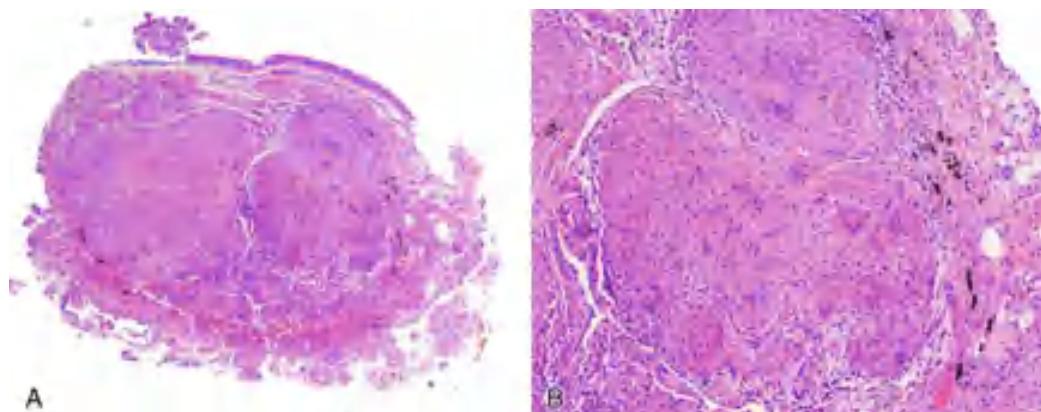


Fig. 448.3 Transbronchial biopsy specimen showing a sarcoid granuloma. A, The granulomas are located below the bronchiolar epithelial layer that appears at the top of the frame. B, A higher-power view of the same biopsy specimen. The epithelioid granuloma is tightly packed and contains multiple multinucleated giant cells. There is no caseous necrosis. Special stains for acid-fast bacilli and fungi were negative. (From Sneller MC, Fontana JR, Shelhamer JH. Immunologic nonasthmatic diseases of the lung. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014: Fig. 62.6.)

Radiology

Pulmonary imaging in sarcoidosis has included plain chest radiography, HRCT of the chest, positron emission tomography using fluorine-18-fluorodeoxyglucose, or radiotracer using gallium-67. The staging of sarcoidosis 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. 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 and traction bronchiectasis from conglomeration of the inflamed tissues. Extensive calcium deposits may be seen at this stage.

HRCT of the chest may be helpful in further staging of the disease and in revealing abnormalities not appreciated on chest radiography. Findings in patients with sarcoidosis by HRCT of the chest 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 therapeutic side effects is imperative. Glucocorticosteroids (GCSs) have long been the mainstay of therapy in sarcoidosis and are often used because of extrapulmonary disease. When pulmonary disease is progressive, GCS therapy is aimed at the 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 before starting GCS therapy.

GCS therapy is often not started in the asymptomatic patient with stage I or II disease. This scrutiny of the benefit of therapy was highlighted when a prospective evaluation of GCS therapy for pulmonary disease found that nearly 50% of patients receiving GCSs had active or relapsing disease 2 years later. In contrast, 90% of patients who did not receive GCSs had spontaneous remission of disease, with the other 10% needing intervention 2 years 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 a total

of 10% or greater, FVC declines 15% or more, or diffusion capacity degradation is noted to be $\geq 20\%$ are all indications for GCS intervention.

Initially, patients are treated with oral prednisone depending on the severity of symptoms. Stability is usually achieved within 6–8 weeks, after which slow, progressive tapering of GCS may occur every 4–8 weeks. Many favor the use of alternate-day steroids to reduce the side effects of GCSs, but little data exist to show efficacy.

For 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 sarcoidosis and review the possibility that beryllium or an infection may be the underlying reason for the progressive disease.

BERYLLOPSIS

Chronic berylliosis disease (CBD), a rare disease, is caused almost exclusively by environmental, and specifically occupational, exposure to beryllium. Examples of these high-risk industries include beryllium and beryllium alloy production, nuclear weapon development, the dental industry, and aircraft/automotive manufacturing. CBD is similar in appearance and pathogenesis to sarcoidosis; however, patients have had a previous exposure to beryllium. Although uncommon in pediatrics, CBD is important to consider in adolescents who work in high-risk industries.

Diagnosis

The most important step in the diagnosis of CBD is establishing a beryllium exposure by performing a thorough history. Special attention should be given to the patient's work history, and in younger children, the work history of the parents, as there are reports of secondary exposure to beryllium causing CBD in at-risk patients. Symptom history is nonspecific, with the most common being dry cough, shortness of breath particularly on exertion, and weight loss. Workplace screening for beryllium sensitization is now implemented in high-risk professions. Given this, the majority of patients are often asymptomatic at the time of diagnosis. The physical exam is also nonspecific in CBD, with most patients having a normal examination; however, crackles and digital clubbing may develop as the disease progresses.

Laboratory testing is a critical step in establishing a diagnosis. Beryllium sensitization is established by performing a beryllium lymphocyte proliferation test (BeLPT). This test is performed by isolating mononuclear cells from patients (either through blood or bronchoalveolar lavage fluid [BALF]) and culturing these cells in different concentrations of beryllium salts. Results are reported as a ratio of stimulated lymphocytes in the beryllium culture versus a control. A BeLPT is considered positive if two or more of the six stimulation indices exceed normal. A diagnosis of beryllium sensitization is confirmed by two positive blood BeLPT tests or one positive BALF BeLPT test. BeLPT screening is performed for employees in high-risk occupations.

Radiography is often obtained but may be nonspecific. Chest x-rays are often not sensitive enough to diagnose CBD. Computed tomography (CT) of the chest reveals a pattern similar to sarcoidosis, with nodules following a bronchovascular distribution. Hilar lymphadenopathy is less common in CBD compared to sarcoidosis. In later stages of the disease, evidence of fibrosis may be seen on the CT scan of the chest.

Pulmonary function testing (PFT) is also commonly performed in the evaluation of CBD. As a result of increased screening with BeLPT, most patients with CBD are now diagnosed before PFT abnormalities become apparent. If PFT abnormalities are noted, these changes are variable, demonstrating an obstructive, restrictive, or mixed pattern. Diffusion capacity for carbon monoxide is often low, especially in advanced disease. Finally, exercise stress testing is also abnormal in advanced CBD.

Bronchoscopy and BAL are important in the evaluation of CBD. BALF often reveals lymphocyte counts above 20%. Furthermore, BeLPT can be performed on BALF, which can confirm beryllium sensitivity. In conjunction with a positive BeLPT and a history of beryllium exposure, lung biopsy is needed to establish a definitive diagnosis of CBD. Biopsy can be obtained either through transbronchial biopsies or surgical lung biopsy. Unlike most pediatric ILDs, transbronchial biopsies are acceptable because of the bronchovascular distribution of CBD. Biopsies reveal noncaseating granulomas with a core of epithelial histiocytes surrounded by a rim of CD4⁺ lymphocytes. Although lung biopsy is essential for diagnosis, a presumptive diagnosis of CBD can be made with a combination of a history of symptoms consistent with CBD, beryllium exposure, beryllium sensitization, PFT abnormalities, radiography changes, and BALF abnormalities.

Treatment

Treatment is not well studied in CBD. Most physicians do not treat asymptomatic patients with normal lung function indices. If lung function declines, first-line therapy is often systemic corticosteroids. Although some patients can stop corticosteroids over time, many will continue to progress without systemic treatment. In patients with persistent disease despite corticosteroids or in those patients who require ongoing treatment and would benefit from steroid-sparing therapy, other medications have been used such as azathioprine, methotrexate, mycophenolate, infliximab, or cyclophosphamide.

GRANULOMATOUS LUNG DISEASE IN PRIMARY IMMUNE DEFICIENCY

Primary immune deficiency (PID) often presents with recurrent or persistent pulmonary symptoms. Patients may experience recurrent infections, pneumonia, bronchiectasis, and ILD with or without fibrosis. Immune dysregulation occurs in many of the PIDs and may manifest with development of granulomatous lung disease and an autoimmune response. Most effort is focused on identifying the infectious pathogens in the PID that may be leading to the pulmonary symptoms; however, immune dysregulation may be the primary problem. This requires counterintuitive therapies with suppression of the immune system concurrently with immune deficiency therapy such as IVIG. The two most prominent PIDs associated with granulomatous lung disease are **chronic granulomatous disease** (see Chapter 170) and **common variable immune deficiency** (see Chapter 166.2).

The classic organism causing granuloma formation in the lung is *Mycobacterium tuberculosis*. Nontuberculous mycobacterial infections also can cause granulomas in the presence of a specific PID. These infections have been seen in patients with defective IL-12, IL-23, and IFN- γ signaling or when there are autoantibodies to IFN- γ . Defective regulation of nuclear factor-kappa B (nuclear factor-kappa B essential modifier defects) have also been reported in patients with nontuberculous mycobacteria. The clinician must be certain that this low-virulence organism is not causing disease before therapy for immune dysregulation is considered. Another PID associated with granulomatous disease involves defects in the INF- γ pathway. These disorders are grouped under the name **Mendelian susceptibility to mycobacterial disease**.

Pathogenesis

In CGD, there are defects in the phagocytic nicotinamide adenine dinucleotide phosphate oxidase system. These defects lead to impairment in

the respiratory burst capacity to generate reactive oxygen species (see Chapter 170).

Patients with CVID have abnormalities in B lymphocytes and hypogammaglobulinemia. Pulmonary manifestations of CVID include organizing pneumonia, ILD, mucosa-associated lymphoid tissue lymphoma, and noncaseating granulomas in **granulomatous and lymphocytic interstitial lung disease (GLILD)** (see Chapter 166.2). Elevated levels of TNF from polymorphisms have been implicated as a possible mechanism. GLILD is becoming recognized more frequently in CVID and other immune disorders. It is defined by the presence of a granulomatous and a lymphocytic proliferative pattern in the lung. Granulomas may be found in other organs, including the bone marrow, spleen, gastrointestinal tract, skin, and liver in GLILD.

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 findings in this subgroup of patients with GLILD 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 additional organ manifestations in the skin, liver, and genitourinary and gastrointestinal tracts. Granulomas are especially problematic in the gastrointestinal and genitourinary tracts. The inhalation of fungal spores and hyphae has led to acute pneumonia in CGD with rapid progression to respiratory failure, with hypoxemia, dyspnea, and fever. This entity, characterized as *mulch pneumonia*, appears to be best treated with antifungal medications and corticosteroids. Patients with GLILD present with progressive exercise intolerance and hypoxemia.

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 of the chest is often mandatory in the initial evaluation of the patients with CVID as a result of nonspecific findings on chest radiograph.

Laboratory and Pulmonary Function Testing

A definitive diagnosis of GLILD is made by lung biopsy with granulomatous disease. 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 testing for infectious organisms) does not contribute significantly to the diagnosis of GLILD. When the child is old enough, complete PFT with spirometry, lung volumes, and diffusion capacity should be obtained at baseline and then followed serially to assess therapeutic response 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 PFT, including spirometry, lung volumes, and diffusing capacity.

448.4 Eosinophilic Lung Disease

Timothy J. Vece and Stephanie D. Davis

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. Collectively, the disorders are often referred to as *pulmonary infiltrates with eosinophilia* and include acute eosinophilic pneumonia, chronic eosinophilic pneumonia, simple eosinophilic pneumonia (also known as *Loeffler eosinophilic pneumonia*), and eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss). The 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 cell count often (but not always) reveals elevated eosinophils, and BALF shows an elevation in eosinophils. Prompt recognition of these diseases allows for lifesaving interventions in idiopathic acute eosinophilic pneumonia (AEP) syndrome or resolution of persistent symptoms in patients with chronic disease.

Etiology

Eosinophilic lung diseases are often classified under two subheadings: idiopathic disease and known causation (Tables 448.8–448.10). They are frequently further subdivided into acute and chronic or infectious and noninfectious. The division of acute or chronic is arbitrary based on the length of symptoms present but is relevant to the clinician in determining the etiology of the symptoms (Table 448.11). Loeffler eosinophilic pneumonia, induced by *Ascaris lumbricoides*, *Strongyloides*, and other ascariids, produces transient symptoms that self-resolve and is classified as neither acute nor chronic.

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 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 with the acute types of eosinophilic pneumonia, where peripheral eosinophilia is often absent; the differential cell count on the BAL is ≥20% eosinophils and is often more than 40%. This highly sensitive and specific 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 BALF. Most commonly, eosinophil-derived neutrotoxin, leukotriene E₄, and 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. **Acute eosinophilic pneumonia** often presents with respiratory failure and the requirement for mechanical ventilation at high levels of positive end expiratory pressure and high concentrations of oxygen, whereas chronic eosinophilic pneumonia has a more indolent presentation (see Table 448.11). Although malignancy (e.g., eosinophilic leukemia) and organizing pneumonia may present with a need for mechanical ventilation, this is uncommon. A history of asthma is common in the chronic eosinophilic pneumonias and in **allergic bronchopulmonary aspergillosis (ABPA)**; it often precedes the diagnosis of these two conditions.

Table 448.8

Key Elements in the Medical History, Laboratory Findings, and Physical Exam to Raise Clinical Suspicion for Diagnostic Testing to Confirm Eosinophilic Lung Disease

MEDICAL HISTORY AND EXAMINATION

- Drug exposure (especially antibiotics, NSAIDs, antiepileptics, antileukotriene modifiers in EGPA)
- Environmental inhalation exposures to dust or inhaled chemicals
- New onset of smoking cigarettes
- Travel or immigration status from areas endemic with various parasites or coccidioidomycosis
- Asthma (may be severe or poorly controlled with ABPA, CSS, or is relatively new in onset with IAEP)
- ABPA concurrent in 7–15% of patients with cystic fibrosis
- Extrapulmonary symptoms suggestive of vasculitis, neuropathy, heart failure, or neoplasm
- Rash (creeping eruption in visceral larval migrans disease or ulceration in EGPA)

DIAGNOSTIC IMAGING AND TESTING

- Radiography helpful in AEP, CEP, and ABPA
 - Radiography not diagnostic in EGPA or drug-induced eosinophilic disease of the lung
- Simple chest radiography findings
 - Nonlobar infiltrate
 - Classic description as mirror image of pulmonary edema with peripheral infiltrates
 - Bilateral pleural effusion in AEP
 - Central bronchiectasis in ABPA
- High-resolution computed tomography of the chest
 - Middle and upper lobe nonlobar infiltrates with areas of ground-glass appearance
 - Mucus plugging in ABPA
 - Central bronchiectasis in ABPA (confused with cystic fibrosis)
- Blood eosinophil count
 - Elevated in many eosinophilic lung diseases
 - Magnitude of eosinophil blood count does not distinguish different pulmonary diseases
 - Not elevated in AEP
 - May occasionally not be elevated in CEP or after use of corticosteroids
- Total serum IgE elevated in ABPA but not always in patients with cystic fibrosis with ABPA
- Serology for helminthic infections or parasites may be diagnostic but are usually not available acutely
- P-ANCA (MPO ANCA) is positive in 40–70% of EGPA (CSS)
- BAL eosinophil percentage
 - ≥25% eosinophils diagnostic in AEP
 - ≥40% eosinophils diagnostic in CEP or tropical pulmonary eosinophilia
 - Eosinophil percentages below these criteria may require lung biopsy
 - <25% eosinophils seen in connective tissue disease, sarcoid, drug-induced disease, histiocytosis X of pulmonary Langerhans cells, and interstitial pulmonary fibrosis

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 antiinflammatory drug; P-ANCA, perinuclear antineutrophil cytoplasmic antibody.

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 granulomatosis with polyangiitis (EGPA)** (formerly known as *Churg-Strauss syndrome*) or **hypereosinophilic syndrome (HES)** should be aggressively investigated.

Chest Imaging

The chest radiograph is one of the most helpful tests for evaluating the child with dyspnea. The characteristic feature of fluffy alveolar

Table 448.9 Classification of the Eosinophilic Pneumonias in Clinical Practice

Eosinophilic Pneumonias of Unknown Cause
Solitary idiopathic eosinophilic pneumonias
Idiopathic chronic eosinophilic pneumonia
Idiopathic acute eosinophilic pneumonia
Eosinophilic pneumonia in systemic syndromes
Eosinophilic granulomatosis with polyangiitis
Idiopathic hypereosinophilic syndrome (lymphocytic or myeloproliferative variant)
Eosinophilic Pneumonias of Known Cause
Allergic bronchopulmonary aspergillosis and related syndromes (including bronchocentric granulomatosis)
Eosinophilic pneumonias of parasitic origin
Eosinophilic pneumonias of other infectious causes
Drug-induced eosinophilic pneumonias
Eosinophilic Airways Diseases
Idiopathic hypereosinophilic constrictive bronchitis
Other Pulmonary Syndromes with Possible (Usually Mild) Eosinophilia
Organizing pneumonia, asthma, idiopathic pulmonary fibrosis, Langerhans cell histiocytosis, malignancies, and so forth

From Cottin V. Eosinophilic lung diseases. *Clin Chest Med.* 2016;37:535–556, Box 1, p. 536.

Table 448.10 Drugs Commonly Causing Eosinophilic Pneumonia

Antiinflammatory drugs and related drugs: acetylsalicylic acid, diclofenac, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, and tolafenamic acid
Antibiotics: ethambutol, fenbufen, minocycline, nitrofurantoin, penicillins, pyrimethamine, sulfamides, sulfonamides, and trimethoprim-sulfamethoxazole
Other drugs: captopril, carbamazepine, and GM-CSF
A more extensive list of drugs reported to cause eosinophilic pneumonia may be found at www.pneumotox.com .

From Cottin V, Cordier JF. Eosinophilic lung diseases. *Immunol Allergy Clin North Am.* 2012;32(4):557–586, Box 6, p. 575.

Table 448.11 Diagnostic Criteria for Idiopathic Chronic Eosinophilic Pneumonia and for Idiopathic Acute Eosinophilic Pneumonia

IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA
1. Diffuse pulmonary alveolar consolidation with air bronchogram and/or ground-glass opacities at chest imaging, especially with peripheral predominance.
2. Eosinophilia at bronchoalveolar lavage differential cell count $\geq 40\%$ (or peripheral blood eosinophils $\geq 1,000/\text{mm}^3$).
3. Respiratory symptoms present for at least 2–4 wk.
4. Absence of other known causes of eosinophilic lung disease (especially exposure to drug susceptible to induce pulmonary eosinophilia).

IDIOPATHIC ACUTE EOSINOPHILIC PNEUMONIA
1. Acute onset with febrile respiratory manifestations (≤ 1 mo, and especially ≤ 7 days duration before medical examination).
2. Bilateral diffuse infiltrates on imaging.
3. Pao_2 on room air $\leq 60 \text{ mm Hg}$ (8 kPa), or $\text{Pao}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$ (40 kPa), or oxygen saturation on room air $< 90\%$.
4. Lung eosinophilia, with $\geq 25\%$ eosinophils at BAL differential cell count (or eosinophilic pneumonia at lung biopsy when done).
5. Absence of determined cause of acute eosinophilic pneumonia (including infection or exposure to drugs known to induce pulmonary eosinophilia). Recent onset of tobacco smoking or exposure to inhaled dusts may be present.

BAL, Bronchoalveolar lavage.

From Cottin V. Eosinophilic lung diseases. *Clin Chest Med.* 2016;37:535–556, Box 2, p. 538.

infiltrates in the peripheral lung field is classic (Fig. 448.4). The images may be easily recognizable by astute clinicians who have identified the etiology of the disease without elevated blood eosinophil counts or BAL.

HRCT of the chest 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 of the chest 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 of the chest is most sensitive in identifying the correct etiology of the disease when chest radiographic findings are nonspecific.

LOEFFLER SYNDROME

The transient pulmonary infiltrates with eosinophilia syndrome that is most often seen in children (formerly known as Loeffler syndrome) is characterized by migrating pulmonary infiltrates with peripheral blood eosinophilia. This syndrome is caused by 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 from areas with poor sanitation, 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 expectorated and swallowed. 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 eosinophilic lung disease. The most common etiologies are the dog roundworm, *Toxocara canis*, but *Toxocara cati*, *Strongyloides stercoralis*, *Baylisascaris procyonis*, and *Lagochilascaris 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 East Asia are regions where paragonimiasis may be found, especially in those who eat raw crabs or crawfish. Many other parasites may have a transient pulmonary syndrome, but their manifestations are most commonly 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 and 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 anthelmintic treatment of other organ disease during the pulmonary phase will increase the inflammatory response in the lung, leading to the need for treatment with corticosteroids.

ACUTE EOSINOPHILIC PNEUMONIA

A unique and dramatic presentation of the eosinophilic pneumonias is AEP (see Table 448.11). AEP mimics infectious pneumonia or acute respiratory distress syndrome with its rapid onset and marked hypoxemia. This disease most frequently occurs in the teenage and young adult populations. 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 weeks after the onset of symptoms. Physical exam demonstrates tachypnea, tachycardia, and crackles in the lung fields. Many patients rapidly deteriorate and require mechanical ventilation.

There is an absence of circulating eosinophilia, which contrasts with the dramatic number of eosinophils seen in the BAL representing at

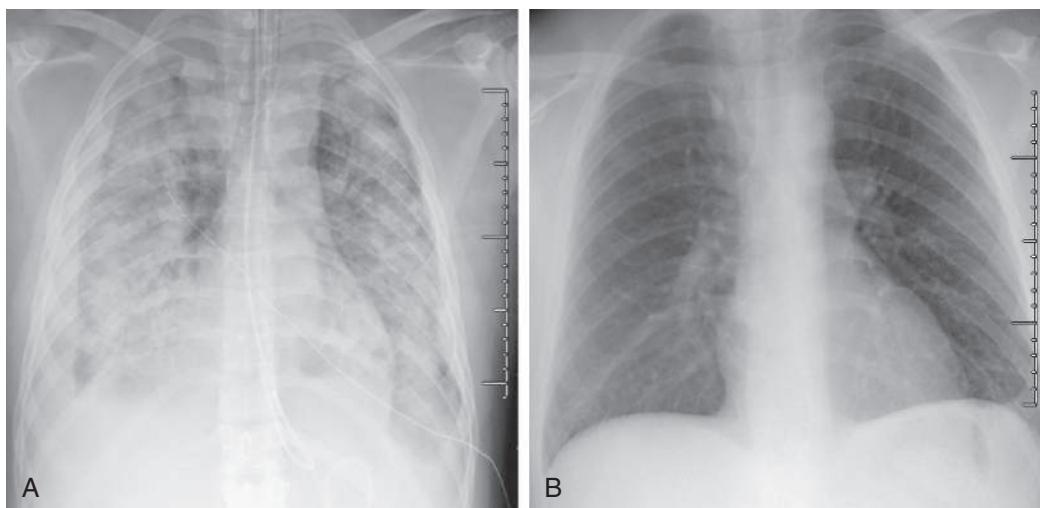


Fig. 448.4 A, Acute eosinophilic pneumonia demonstrating the mirror image pulmonary edema with a right pleural effusion on admission. B, Complete clearing upon discharge from the hospital after corticosteroid usage.

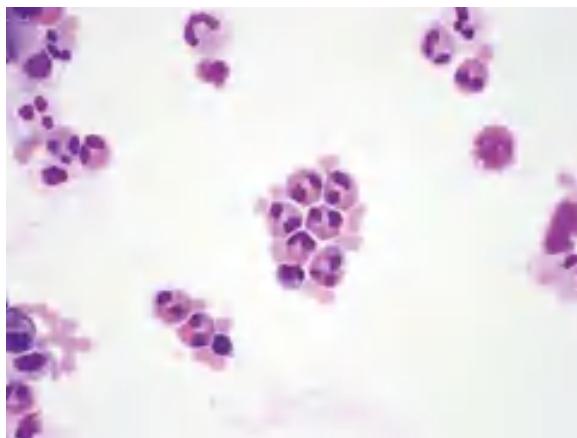


Fig. 448.5 Light microscopy of eosinophils in bronchoalveolar lavage fluid.

least 20% of the inflammatory cells (often 40–55%) (Fig. 448.5). 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 the onset of smoking tobacco, change in smoking frequency, reinitiation of smoking in young male adolescents or adults, and even massive secondary smoke exposure as critical associations with the 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 should educate the patient and family about the link to smoking exposure and the risk of AEP upon reexposure.

In addition to smoke exposure, AEP has been reported after smoking cocaine; typically, within hours to days after use. 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 hours of cocaine smoke inhalation.

Lung function has not been measured frequently in the disease because the patients have proceeded rapidly to the intensive care unit (ICU) for mechanical ventilation. When measured, a restrictive pattern of lung disease and reduced diffusion capacity are the usual findings.

Arterial blood gases will also show a significant increase in the alveolar-arterial gradient.

The criteria for diagnosis include the acute onset of disease, bilateral pulmonary infiltrates, reduced oxygen saturation or $\text{PaO}_2 \leq 60$ mm Hg, BAL of $\geq 25\%$ eosinophils, and absence of a determined cause of eosinophilia (see Table 448.11). The recent onset of tobacco exposure, dust, or chemical inhalation are supporting factors in confirming a diagnosis.

Treatment has uniformly been the use of a corticosteroid (e.g., methylprednisolone 1–2 mg/kg/day) either intravenously or orally. A minimum or maximum treatment time has not been determined. Rare fatalities have been reported. Complete recovery has been seen in days, with resolution of pleural effusions within 4 weeks of treatment. Most important, relapse and persistent symptoms are rare, which sharply contrasts with the idiopathic chronic eosinophilic pneumonias. Follow-up testing of pulmonary function is 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) and usually in patients who are non-smokers. Chest examination reveals tachypnea, crackles, and wheezing; a diagnosis of asthma is a common finding. The classic finding on chest x-ray of the *radiographic negative of pulmonary edema* is found in these patients: central clear lung fields but fluffy, patchy peripheral infiltrates; however, this is not seen in all cases.

When compared to AEP, the onset of disease is indolent and subtle, but the accompanying fever and weight loss may lead the clinician toward a concern for an underlying malignancy before the chest radiograph and laboratory investigation. *Peripheral* blood eosinophilia is commonly as high as $5,000/\text{mm}^3$ or greater, accompanied by BAL eosinophilia $>40\%$ on the differential count (see Table 448.11). The peripheral eosinophilia sharply contrasts with the lack of eosinophils seen in the blood in AEP. HRCT scan of the chest contrasts with the AEP, with pleural effusion as a rare finding, as well as rare cavitation.

In contrast to AEP, PFT shows a mixed obstructive and restrictive pattern, especially given that asthma often occurs concurrently with this disease.

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 IL-18. However, T-lymphocyte type 1 cytokines of IL-2 and IL-12 are also present with many of the potent eosinophilic chemoattractants 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 weeks. The dose is reduced to half (0.025 mg/kg/day) for an additional 2 weeks if symptoms have abated. The remaining dose of steroid may need to be weaned over 6 months. Alternatively, IV methylprednisolone is used, starting with 10–30 mg/kg/dose (maximum 1 g) given either 3 consecutive days per month or 1 day per week. Symptoms and pulmonary infiltrates rapidly disappear after initiation of this treatment but frequently recur with tapering of the steroid. Asthma that occurs concurrently in patients with chronic eosinophilic pneumonia represents 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 EGPA (formerly Churg-Strauss syndrome). The utility of ICS in chronic eosinophilic pneumonia is unknown but is warranted for the persistent asthma phenotype of the disease. A subset of patients develops permanent lower airway obstruction without reversibility, which requires patients with this disease to have close follow-up and monitoring of pulmonary function tests.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS SYNDROME)

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/ μ L) in the blood. Evidence of vasculitis must be present in at least two 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 (Table 448.12). Rhinitis and upper airway disease are present in 75% of the patients but are not specific. Symptoms 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 screening should occur for these manifestations. The multiple organ involvement results in the morbidity and mortality of this disease. The typical progression of the disease is in three phases: rhinitis and asthma first, tissue eosinophilia second, and, finally, systemic vasculitis of small and medium vessels.

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 the use of corticosteroids leading to the full-blown (unmasking) manifestation of EGPA. Many refrain from use of leukotriene-receptor antagonists when EGPA syndrome has been diagnosed.

Clinical and laboratory findings pinpoint the diagnosis with high specificity (99.7%) and sensitivity (85%) when at least four of six criteria developed by the American College of Rheumatology are met (asthma, eosinophilia >10%, mononeuropathy or polyneuropathy, 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 or HRCT of the chest demonstrates migratory, peripheral predominant opacities, ground-glass appearance, nodules, bronchiectasis, and bronchial wall thickening. 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 vasculitis activity. The BAL shows striking eosinophilia with differential counts often >60%. Biopsies of other organ systems reflect the activity of eosinophils and are not specific for the EGPA diagnosis.

ANCA may be present in EGPA syndrome. The perinuclear ANCA targeting myeloperoxidase is 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-ANCA (see Table 448.12).

Pulmonary function tests show an obstructive pattern caused by the asthma component. The pulmonary obstruction is responsive to oral corticosteroid use, but often mild obstruction persists.

Treatment of EGPA with systemic oral corticosteroids remains the mainstay of therapy at a starting dose of 0.5 to 1 mg/kg/day. This therapy is often required for up to 12 months or longer, with a steady taper in dosage over that time. EGPA resistant to corticosteroids has responded to cyclophosphamide, IFN- α , cyclosporine, IVIG, and plasmapheresis. The use of anti-IL-5 (mepolizumab) has been encouraging and may be used as a steroid-sparing agent in the future.

Table 448.12 | Eosinophilic Granulomatosis with Polyangiitis

	VASCULITIC PHENOTYPE	EOSINOPHILIC TISSULAR DISEASE PHENOTYPE
Respective frequency	~40%	~60%
ANCA	Present (mostly perinuclear-ANCA with anti-MPO specificity)	Absent
Predominant manifestations	Glomerular renal disease Peripheral neuropathy Purpura Biopsy-proven vasculitis	Cardiac involvement (eosinophilic myocarditis) Eosinophilic pneumonia Fever

ANCA, Antineutrophil cytoplasmic antibody; MPO, myeloperoxidase.

Data from Sablé-Fourtassou R, Cohen P, Mahr A, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med.* 2005;143:632–638; and Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum.* 2005;52:2926–2935.

From Cottin V, Cordier JF. Eosinophilic lung diseases. *Immunol Allergy Clin North Am.* 2012;32(4):557–586, Table 2, p. 569.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA is a complex hypersensitivity reaction that occurs in the lungs and bronchi in response to exposure and colonization of *Aspergillus* species (usually *Aspergillus fumigatus*; see Chapter 283). This disease occurs in patients with preexisting asthma and up to 15% of patients with cystic fibrosis (see Chapter 454). The quantity of *Aspergillus* exposure does not correlate with the severity of disease.

The clinical pattern of disease (Table 448.13) is remarkably similar with a presentation of difficult-to-treat asthma. The patient suffers from 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 antibodies to *Aspergillus* species, and proximal bronchiectasis. Other clinical manifestations include dyspnea, cough, shortness of breath, and peripheral eosinophilia, along with pulmonary eosinophilia seen on BAL with infiltration of the parenchyma. The use of systemic corticosteroids may lower the total IgE antibody levels such that a diagnosis may be in question when the initial tests are conducted.

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 antibodies, precipitating antibodies to *A. fumigatus*, and/or new abnormalities on chest radiography that fail to clear with antibiotics should alert the clinician to the possibility of ABPA.

Table 448.13 Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS—CENTRAL BRONCHIECTASIS

- Medical history of asthma*
- Immediate skin prick test reaction to *Aspergillus* antigens*
- Precipitating (IgG) serum antibodies to *Aspergillus fumigatus**
- Total IgE concentration >500 IU/mL (>1,000 ng/mL)*
- Central bronchiectasis on chest CT*
- Peripheral blood eosinophilia >500/mm³
- Lung infiltrates on chest x-ray or chest HRCT
- Elevated specific serum IgE and IgG to *A. fumigatus*

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS SEROPOSITIVE†

- Medical history of asthma†
- Immediate skin prick test reaction to *A. fumigatus* antigens†
- Precipitating (IgG) serum antibodies to *A. fumigatus*†
- Total IgE concentration >417 IU/mL (>1,000 ng/mL)†

*The criteria required for a diagnosis of ABPA with central bronchiectasis.

†The first four criteria are required for a diagnosis of seropositive ABPA.

ABPA, Allergic bronchopulmonary aspergillosis; CSD, corticosteroid dependent; HRCT, high-resolution computed tomography.

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 conducted. The absence of a positive skin prick test and intradermal test to *A. fumigatus* 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.

Patients with cystic fibrosis who are less than 6 years of age rarely develop ABPA. When the total IgE antibody in patients with cystic fibrosis exceeds 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 granulomas. Histologic features characteristic of asthma are also present. Septated hyphae are often found in the mucus-impacted bronchial tree. However, the fungi are not invasive in this unique disease. *Aspergillus* may be cultured from sputum in more than 60% of patients. Interestingly, hyphae may not be detected on microscopy.

Staging of the disease (Table 448.14) represents distinct phases; however, progression does not necessarily occur 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 to screen 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 not accompanied by changes in symptoms in approximately 25% of the recurrences, serial IgE accompanied by chest radiography is 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. 448.6). HRCT of the chest demonstrates central bronchiectasis (Fig. 448.7) and mucus impaction of the airways (finger-in-glove appearance). HRCT may add value for the patient with a positive skin prick test and normal chest radiograph to detect characteristic abnormalities of ABPA.

Treatment

The mainstay of therapy for ABPA has been systemic glucocorticoids with adjunct therapy including antifungal medications and anti-IgE therapy with omalizumab. Exacerbations in stages 1 and 3

Table 448.14 Staging of Allergic Bronchopulmonary Aspergillosis

Stage 1	Acute	Upper and middle lobe infiltration	High IgE
Stage 2	Remission	No infiltrate off steroids >6 mo	Normal to high IgE
Stage 3	Exacerbation	Upper and middle lobe infiltration	High IgE
Stage 4	CSD asthma	Minimal infiltrate	Normal to high IgE
Stage 5	End stage	Fibrosis and/or bullae	Normal

CSD, Corticosteroid dependent.

may be treated for 14 days with 0.5–1 mg/kg of glucocorticoids followed by every-other-day usage and tapering over 3 months or as long as 6 months. 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-week course of itraconazole improves the response rate during exacerbations, allowing the reduction of glucocorticoid dosage by 50% and resulting in 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 corticosteroid serum levels by slowing the metabolism of the steroid. This latter mechanism would be true for prednisone, which is methylated in the liver, but not for methylprednisolone, which does not require methylation.

The adult dosage recommendation for itraconazole is 200 mg 3 times per day for 3 days followed by 200 mg twice daily for the remainder of the 16 weeks. Children should receive 5 mg/kg/day in a single dose. If the proper calculated dose exceeds 200 mg, then the total dose should be divided equally and given twice daily. Serum levels of itraconazole are necessary to ensure proper drug absorption when in capsule form.

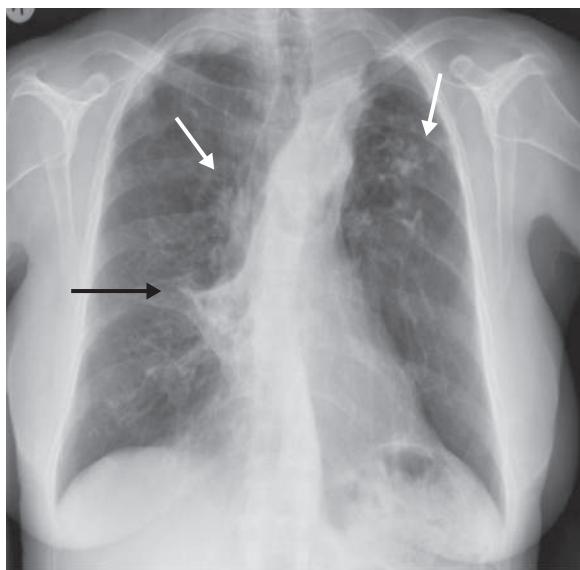


Fig. 448.6 Transitory opacities (white arrows) and lobar collapse (black arrow) in patient with allergic bronchopulmonary aspergillosis. (From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE. Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014: Fig. 61.2.)

The liquid form is more readily absorbed and has achieved substantially higher levels. The use of proton pump inhibitors and histamine 2 antagonists may reduce absorption of itraconazole. Voriconazole has been used as a substitute antifungal medication. Proper dosing has been established for invasive *Aspergillus* disease but not for ABPA. Hepatotoxicity may occur with these drugs so liver function must be monitored.

Omalizumab, an anti-IgE humanized monoclonal antibody, has been used in a case series of patients with cystic fibrosis and ABPA and in a small cohort of adults without cystic fibrosis but with ABPA. Both case series demonstrated significant reductions in asthma exacerbations, ABPA exacerbations, and glucocorticoid usage. The dose prescribed has been 300–375 mg every 2 weeks by subcutaneous injection.

HYPEREOSINOPHILIC SYNDROME

See Chapter 169.

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 448.15). Specific

Table 448.15 Hypereosinophilic Syndrome Variants

Myeloproliferative	Nonclonal Clonal–F1P1L1/PDGFRα-positive chronic eosinophilic leukemia
Lymphocytic	Nonclonal T cells Clonal T-cell expansion with T-cell activation
Overlap	Organ restricted
Familial	Family history of eosinophilia without known cause
Associated	Eosinophilia in chronic disease like inflammatory bowel disease or EGPA (Churg-Strauss syndrome)
Undefined	Asymptomatic Cyclic angioedema with eosinophilia (Gleich syndrome) Symptomatic without myeloproliferation or lymphocytic form

EGPA, Eosinophilic granulomatosis with polyangiitis; PDGFRα, platelet-derived growth factor receptor-α.

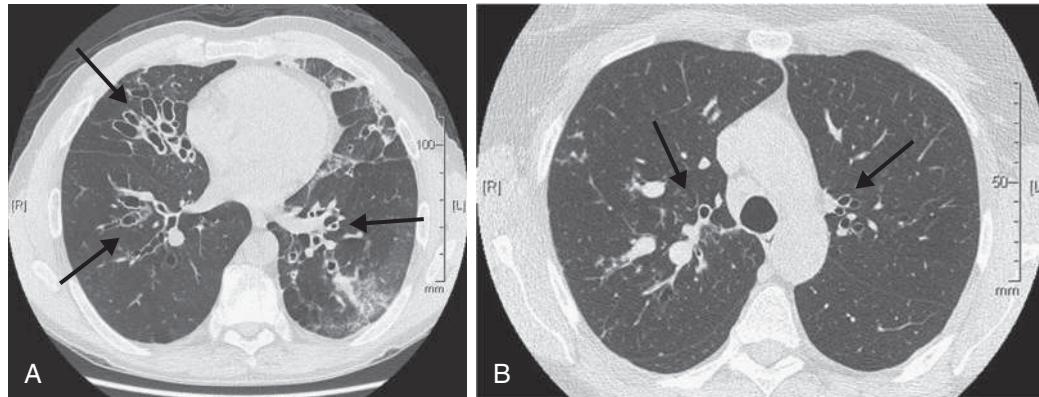


Fig. 448.7 A, Central bronchiectasis in patient with ABPA (arrows). B, Central bronchiectasis in the upper lobes (arrows). (From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE. Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson NF Jr, Bochner BS, Burks AW, et al., eds. Middleton's Allergy Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014: Fig. 61.3.)

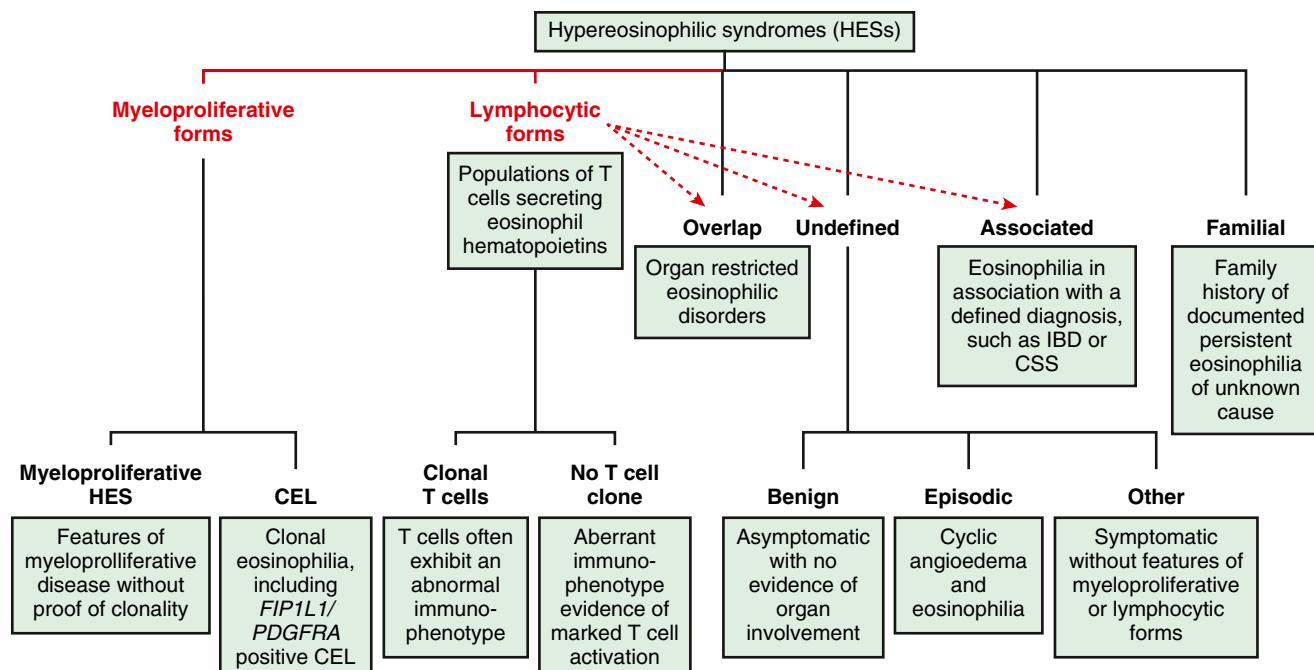


Fig. 448.8 A revised classification of hypereosinophilic syndrome (HES). Changes from the previous classification are indicated in red type. Dashed arrows identify HES forms in some patients who have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin-producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. (From Simon H, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010;126:45–49, Fig. 1.)

syndromes such as EGPA have eosinophilia, but the contribution of eosinophils to the organ damage is incompletely understood.

Some variants of HES have pathogenic variants in tyrosine kinase receptor platelet-derived growth factor receptor- α (*PDGFRA*); males are almost exclusively affected. *PDGFRA* can also form a fusion gene with *FIP1L1* in some patients with HES. Patients with *PDGFRA-FIP1L1* are more likely to be responsive to imatinib, a tyrosine kinase inhibitor. Otherwise, HES appears to be distributed equally among females and males.

Hypereosinophilia is defined as an absolute eosinophil number in the blood that exceeds 1.5×10^9 eosinophils on two separate occasions separated by at least 1 month and/or a tissue diagnosis of hypereosinophilia. Tissues are abnormal when more than 20% of nucleated cells in the bone marrow are of eosinophil origin, a pathologist determines the presence of eosinophilia, or the presence of extensive eosinophilic granule proteins are determined on biopsy to be deposited in large quantities. These disorders can be subclassified into primary (neoplastic), secondary (reactive), and idiopathic (Fig. 448.8).

Clinical manifestations of HES include organ involvement of the heart (5%), gastrointestinal tract (14%), skin (37%), and respiratory system (25–63%). 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 that leads the clinician to a high index of suspicion for 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 two biomarkers are most frequently elevated when the *FIP1L1-PDGFR^A* fusion pathogenic variant is present.

Because of the extensive pulmonary disease that is seen in HES, pulmonary function tests (spirometry, lung volumes) should be performed at diagnosis. Dead space ventilation may be significantly elevated in patients with pulmonary emboli. Pulse oximetry may be helpful in the evaluation as well.

Chest radiography and CT of the chest are 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/ μ L, and vascular insufficiency symptoms. Prednisone is indicated to acutely reduce the eosinophil count after diagnostic tests are performed and 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. Imatinib is especially used in patients found to have the *FIP1L1-PDGFR^A* fusion variant.

When eosinophil counts are not as dramatically elevated, therapy begins with glucocorticoids at 1 mg/kg for patients who do not have the *FIP1L1-PDGFR^A* variant. Patients with this variant are resistant

to glucocorticoids, and initial treatment should begin with imatinib, a tyrosine kinase inhibitor. In cases where genetic testing for *FIP1L1-PDGFRα* is not readily available, surrogate markers for the presence of this variant are vitamin B₁₂ levels >2,000 pg/mL or serum tryptase >11.5 ng/mL. These findings denote the presence of resistant disease that should initially be treated with imatinib. The goal of therapy is to reduce and maintain eosinophil counts below 1.5×10^9 at the lowest dose of prednisone possible to reduce or avoid corticosteroid-related side effects. If corticosteroid doses cannot 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, IFN- α , anti-IL-5 monoclonal antibody therapy, and a monoclonal antibody directed against CD52. Failure of these modalities may signal a need for hematopoietic stem cell transplantation. This therapy has been successful in some patients.

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448.5 Interstitial Lung Disease

Timothy J. Vece and Stephanie D. Davis

Interstitial lung disease in children (chILD) is caused by a large group of rare, heterogeneous, familial, or sporadic diseases that involve the pulmonary parenchyma and cause significant impairment of gas exchange (Tables 448.16–448.18). Although there are some shared diseases, childhood ILD is often different from ILD in adults, especially notable for the absence of IPF in children. Furthermore, certain ILDs only occur in children (e.g., neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenosis). Despite wide variations in cause, these disorders are classified together because of the similar clinical, physiologic, radiographic, and pathologic processes involving disruption of the alveolar interstitium and/or airways. Prevalence estimates vary widely with a range of 0.13–16.2 cases/100,000 children. This large range in prevalence is likely a result of the lack of standardization of the diseases that are included in the definition of ILD in children. The pathophysiology is 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. Genetic causes of ILD are becoming increasingly important, especially the disorders of surfactant metabolism (DSM) and immune dysregulatory disorders.

CLASSIFICATION AND PATHOLOGY

Through the work of the children's ILD research network in the United States and the children's ILD-European Union group, consensus on a classification scheme has been reached. The classification is broken down based on histologic pattern and by age, with 2 years of age serving as a cutoff. The classification scheme was first applied to biopsies from children less than 2 years of age and was later extended to children greater than 2 years of age (see Tables 448.16 and 448.17). Growth disorders such as alveolar simplification, unique diseases of infancy such as neuroendocrine cell hyperplasia of infancy (NEHI), and disorders of surfactant metabolism (DSM) are common in children less than 2 years of age. In contrast, disorders of the immunocompromised host, such as ILD related to immune deficiency, and disorders of systemic diseases such as the collagen vascular disorders, are much more common in older children.

Neuroendocrine Cell Hyperplasia of Infancy

See Chapter 448.6.

Table 448.16 The Pediatric Interstitial Lung Diseases in Children Under 2 Years of Age

AGE-RELATED INTERSTITIAL LUNG DISEASES IN INFANCY AND EARLY CHILDHOOD

- Diffuse developmental disorders
 - Acinar dysplasia
 - Congenital alveolar dysplasia
 - Alveolar capillary dysplasia with misalignment of pulmonary veins (some caused by *FOXF1* pathogenic variants)
- 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 variant
 - Surfactant protein C variant
 - ABCA3 variant
 - Granulocyte-macrophage colony-stimulating factor receptor (*CSF2RA*) variant
 - NKX2.1 (transcription factor for SP-B, SPC, ABCA3)

INTERSTITIAL LUNG DISEASE DISORDERS WITH KNOWN CAUSES

Infectious/postinfectious processes

- Adenovirus viruses
- 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 interstitial lung disease associated with common variable immunodeficiency syndrome
- Lymphoid intestinal pneumonia (HIV infection)

Therapeutic interventions: chemotherapy, radiation, transplantation, and rejection

IDIOPATHIC INTERSTITIAL LUNG DISEASES

- Desquamative interstitial pneumonitis
- 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 vascular disorders
- Pulmonary lymphatic disorders
- Pulmonary microlithiasis

SYSTEMIC DISORDERS WITH PULMONARY MANIFESTATIONS

- Anti-GBM disease
- Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Idiopathic pulmonary capillaritis
- Gaucher disease and other storage diseases
- Malignant infiltrates
- Hemophagocytic lymphohistiocytosis
- Langerhans cell histiocytosis
- Sarcoidosis
- Systemic sclerosis
- Polymyositis/dermatomyositis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Lymphangioleiomyomatosis
- Pulmonary hemangiomatosis
- Neurocutaneous syndromes
- Hermansky-Pudlak syndrome

Modified from Deutsch GH, Young LR, Deterding RR, et al. Diffuse lung disease in young children: application of a novel classification scheme. *Am J Respir Crit Care Med.* 2007;176:1120–1128.

Table 448.17 The Pediatric Interstitial Lung Diseases in Children over 2 Years of Age

DISORDERS OF THE IMMUNOCOMPETENT HOST

Disorders of Infancy

Growth abnormalities

NEHI

Disorders of surfactant metabolism

Systemic Disease

Immune-mediated disorders

- Connective tissue disease related lung disease
- Pulmonary hemorrhage syndromes

Storage diseases

Sarcoidosis

DISORDERS OF THE IMMUNOCOMPROMISED HOST

Opportunistic infections

Related to treatment

- Chemotherapy
- Radiation

Drug hypersensitivity

Related to transplantation

- Rejection
- GVHD
- PTLD

Lymphoid Infiltrates

GVHD, Graft-versus-host disease; NEHI, neuroendocrine cell hyperplasia of infancy; PTLD, posttransplant lymphoproliferative disease.

Modified from Fan LL, Dishop MK, Galambos C, et al. Diffuse lung disease in biopsied children 2 to 18 years of age. Application of the chILD Classification Scheme. *Ann Am Thorac Soc*. 2015;12(10):1498–1505.

Disorders of Surfactant Metabolism

One of the more important groups of disorders in childhood ILD is the **DSM** (Table 448.19). These disorders likely account for previously unknown cases of neonatal respiratory distress in full-term infants. Surfactant protein B deficiency, caused by pathogenic variants in the surfactant protein B gene, leads to severe neonatal respiratory distress. Chest CT imaging often reveals a pattern of diffuse ground-glass opacities with septal thickening. Histopathology reveals alveolar proteinosis with interstitial widening, and electron microscopy shows disorganized lamellar bodies. Most children die within the first 2 months of life without a lung transplant. Surfactant protein C deficiency can cause disease in older infants, children, or adults. Chest CT imaging reveals diffuse ground-glass opacities with septal thickening early in the disease or significant fibrosis and honeycombing with cyst formation in more advanced disease. Histopathologic findings vary with age, with alveolar proteinosis and interstitial widening seen in young children, and fibrosis seen in older children and adults. Electron microscopy reveals normal lamellar bodies. *ABCA3* variants cause variable lung disease in children, with some having severe disease similar to surfactant protein B deficiency, whereas others have less severe disease similar to surfactant protein C. Chest CT imaging most often reveals diffuse ground-glass opacities with septal thickening early in the disease (Fig. 448.9). Histopathology depends on the age of the child; however, electron microscopy shows characteristic changes in the lamellar bodies with an eccentric electron dense body without the characteristic concentric circles, the so-called *fried egg appearance*. **DSM** caused by pathogenic variants in the gene *NKX2.1* has also been described. *NKX2.1* encodes for thyroid transcription factor 1 (TTF-1), which is a major regulator of surfactant protein transcription. Pathogenic variants in *NKX2.1* cause variable disease in the lungs, brain, and thyroid (**brain-lung-thyroid syndrome**) (see Table 448.19). Lung disease is variable and can present similar to surfactant protein B deficiency, similar to surfactant protein C

deficiency, or as recurrent pulmonary infections. Finally, variants in the α and β subunits of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor leads to alterations in surfactant catabolism. Alveolar macrophages are critical for surfactant recycling and are unable to perform this function effectively in patients with these variants. The inability to recycle surfactant leads to subsequent accumulation of proteinaceous material and pulmonary alveolar proteinosis.

Interstitial Lung Disease Due to Systemic Disease

ILD due to systemic disease is more common in older children with diffuse lung disease. The most common lung disease seen on biopsy is nonspecific interstitial pneumonia; however, other patterns are seen depending on the underlying disorder. For example, lymphocytic interstitial pneumonia may be seen in Sjögren syndrome or cryptogenic organizing pneumonia in dermatomyositis. Findings on chest CT scans depend on the underlying ILD, with nonspecific interstitial pneumonia revealing areas of ground-glass opacities and septal thickening in the early cellular phase of the disease (Fig. 448.10) and progressing to diffuse fibrosis with traction bronchiectasis and peripheral cysts in the later fibrotic stage of the disease. The exact mechanism for disease is unknown but likely is caused by autoantibodies to respiratory tissue.

Pulmonary vasculitis, either caused by granulomatosis with polyangiitis, microscopic polyangiitis, idiopathic pulmonary capillaritis, or anti-GBM syndrome (formerly Goodpasture disease), is another common manifestation of systemic diseases. The disease is likely the result of autoantibody stimulation of lymphocytes with resultant inflammation of pulmonary endothelium causing interstitial changes and pulmonary hemorrhage. Histopathology reveals diffuse alveolar hemorrhage, interstitial widening, and with the exception of anti-GBM disease, neutrophilic inflammation of the pulmonary vasculature.

Genetic causes of immune dysregulation may also be responsible for ILD in children. Pathogenic variants in both *STAT3b* and *LRBA* have been shown to cause lymphocytic interstitial pneumonia and lymphoproliferative disease. Pathogenic variants in coatomer-associated protein-alpha (*COPA*), a protein involved in endoplasmic reticulum to Golgi transport, cause familial pulmonary hemorrhage and/or ILD.

Persistent pulmonary symptoms can occur after respiratory infections caused by adenoviruses, influenza viruses, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. The resultant pulmonary disease is called **bronchiolitis obliterans** and is characterized by obstructive lung disease and obliteration or constriction of the bronchioles on lung biopsy. There is a characteristic appearance on HRCT of the chest with mosaicism, vascular attenuation, and central bronchiectasis, which if present, can obviate the need for lung biopsy (Fig. 448.11). Aspiration is a frequent cause of chronic lung disease in childhood and can mimic ILD. 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 (GER). An undiagnosed tracheoesophageal fistula can also result in pulmonary complications related to aspiration of gastric contents leading to 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, an opportunistic infection, or related 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. One should also ask about any family history of lung disease. Identification of precipitating factors, such as exposure to

Table 448.18 Pathogenic Variants Associated with Children's Interstitial and Diffuse Lung Disease

DISORDER (GENE)	INHERITANCE	CLINICAL PRESENTATION	TREATMENT APPROACH
ABCA3 deficiency (ABCA3)	Autosomal recessive	Loss of functional protein causes severe respiratory failure in newborn babies or gradual development of respiratory symptoms in older children and adults	Reported responses to immune suppression with hydroxychloroquine; azithromycin; lung transplantation considered
COPA syndrome (COPA)	Autosomal dominant	Autoimmune interstitial lung, joint, and kidney disease arising in the first 2 decades of life	Janus kinase inhibitors; lung transplantation considered
Pulmonary alveolar proteinosis (colony stimulating factor 2 receptor α [CSF2RA])	X-linked	Primary PAP; dyspnea and cough in early childhood	Whole lung lavage
Pulmonary alveolar proteinosis (colony-stimulating factor 2 receptor β [CSF2RB])	Autosomal recessive	Primary PAP; dyspnea and cough in early childhood	Whole lung lavage
Filamin A syndrome (FLNA)	X-linked recessive	Dyspnea in infancy	Symptomatic; lung transplantation considered
Alveolar capillary dysplasia with misalignment of the pulmonary veins (FOXF1)	Autosomal dominant (usually with paternal imprinting)	Acute respiratory distress within first few hr of birth; without transplant few survive to 1 yr	Lung transplantation considered
Immunodeficiency 21: profound deficiency with pulmonary alveolar proteinosis (GATA2)	PAP form is autosomal dominant	Profound B-cell loss with normal T-cell numbers leads to opportunistic infection and PAP	Hematopoietic stem cell transplantation
Interstitial lung and liver disease (MARS[methionyl-tRNA synthetase])	Autosomal recessive	Failure to thrive, hypotonia, intermittent lactic acidosis, severe cirrhosis, respiratory failure (PAP), and interstitial lung disease in infancy or early childhood	Symptomatic; whole lung lavage considered
Brain-lung-thyroid syndrome (NKX2-1)	Autosomal dominant	Infant respiratory distress and recurrent pulmonary infection with associated hypothyroidism and neurologic impairment	Symptomatic; lung transplantation considered
Lung disease, immunodeficiency, and chromosome breakage syndrome (NSMCE3)	Autosomal recessive	Failure to thrive in infancy with immunodeficiency and viral-induced fatal lung disease	Hematopoietic stem cell transplantation
Infantile-onset pulmonary alveolar proteinosis (OAS1)	Autosomal dominant	Onset of dyspnea and respiratory distress often associated with a viral infection; hypogammaglobulinemia and splenomegaly	Hematopoietic stem cell transplantation
Surfactant protein B deficiency (SFTPB)	Autosomal recessive	Acute neonatal fatal respiratory distress; some reports of dyspnea in older children	Symptomatic; lung transplantation considered
Surfactant protein C mutation (SFTPC)	Autosomal dominant	Acute neonatal respiratory distress, but also presents in older children and adults	Consider corticosteroids and hydroxychloroquine; lung transplantation considered in severe or progressive cases
Lysinuric protein intolerance (SLC7A7)	Autosomal recessive	Short stature, hepatosplenomegaly; recurrent infection; early childhood respiratory failure in some (PAP); pulmonary fibrosis in a third in later life	Poor response to GMCSF; low-protein diet and citrulline supplementation
Acinar dysplasia (TBX4)	Autosomal dominant	Acute fatal neonatal respiratory insufficiency; patellar aplasia or hypoplasia syndrome; pulmonary arterial hypertension	Lung transplantation considered
STING associated vasculopathy with onset in infancy (TMEM173)	Autosomal dominant	Infant-onset systemic inflammation with skin lesions, vasculopathy, and pulmonary fibrosis	Janus kinase inhibitors

PAP, Pulmonary alveolar proteinosis; GMCSF, granulocyte-macrophage colony-stimulating factor.

From Cunningham S, Jaffe A, Young LR. Children's interstitial and diffuse lung disease. *Lancet Child Adolesc*. 2019;3:568–577.

Table 448.19 Clinical Features, Age, and Onset of Surfactant Protein Dysfunction Syndromes (SPDS)

SPDS	CLINICAL FEATURES	AGE AND ONSET
SFTPB	Neonatal • Respiratory distress	Neonate, acute
ABCA3	Neonatal • Respiratory distress Infancy • Cough • Tachypnoea, hypoxemia • Failure to thrive Childhood • Wheeze, crackles • Exercise intolerance • Dyspnea • Retractions, crackles, digital clubbing • Low body weight	Neonate, acute Infancy and childhood, subacute Late childhood and adulthood, chronic
SFTPC	Neonatal • Respiratory distress Childhood • Cough • Tachypnea, hypoxemia	Neonate, acute (infrequent) Infancy and childhood, subacute Late childhood and adulthood, chronic
NKX2.1	Respiratory • Neonatal respiratory distress • Recurrent infections • Chronic interstitial lung disease Neurologic • Chorea • Ataxia • Developmental delay • Hypotonia • Hypothyroidism	Any age Acute or chronic
GMCSFR	Infancy Respiratory distress Cough	Infancy Chronic
Anti-GMCSF antibodies	Respiratory Cough Exercise intolerance Hypoxemia	Teenage years Chronic

ABCA3, ATP binding cassette number A3.

From Gupta A, Zheng SL. Genetic disorders of surfactant protein dysfunction: when to consider and how to investigate. *Arch Dis Child*. 2017;102:84–90, Table 2, p. 86.

molds or birds and a severe lower respiratory infection, is important in establishing the diagnosis and instituting potential avoidance measures. Patients may develop hypoxia and hypercarbia. Tachypnea, crackles on auscultation, retractions, and digital clubbing may be noted on physical examination in children with ILD. However, chest physical examination findings can be normal. Failure to thrive, likely because of increased work of breathing leading to high caloric needs, is also common in ILD. Wheeze and fever are less common but have been noted in childhood ILD, especially in bronchiolitis obliterans. 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.

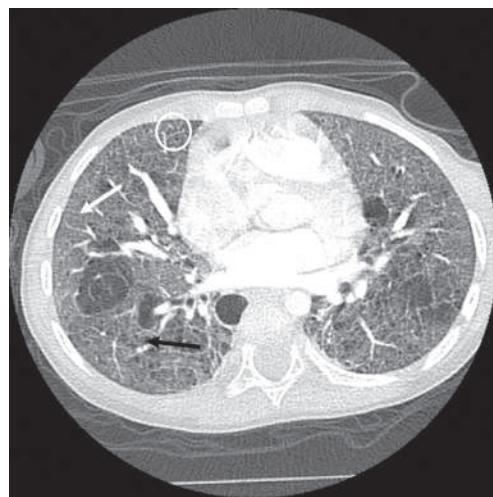


Fig. 448.9 Chest CT from a 2-year-old with a disorder of surfactant metabolism from pathogenic variants in ABCA3. Note the ground-glass opacities (white arrow), septal thickening (circle), and early cyst formation (black arrow). (Courtesy R. Paul Guillerman, MD.)



Fig. 448.10 Chest CT from an 11-yr-old patient with systemic sclerosis and cellular nonspecific interstitial pneumonia. Note the areas of ground-glass opacities in the periphery (arrows). (Courtesy R. Paul Guillerman, MD.)

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. Chest CT imaging may reveal 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 respiratory dysfunction and in following the response to treatment. In ILD, pulmonary function abnormalities demonstrate a restrictive ventilatory deficit with decreased lung volumes and reduced

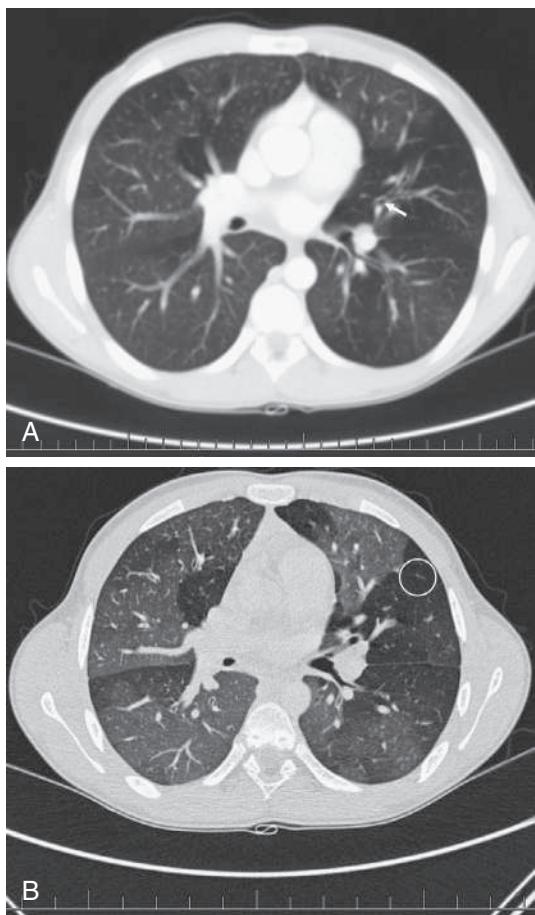


Fig. 448.11 Chest CT from an 11-yr-old patient with bronchiolitis obliterans after Stevens-Johnson syndrome. **A**, Volumetric scan at full inspiration shows central bronchiectasis (arrow) and mosaic attenuation. **B**, High-resolution image taken in exhalation better highlights the mosaic attenuation and vascular attenuation (circle).

lung compliance. However, obstructive impairment may be seen in some forms of ILD such as bronchiolitis obliterans. The functional residual capacity is often reduced but is usually less affected than vital capacity and total lung capacity (TLC). The residual volume (RV) is usually maintained; therefore ratios of functional residual capacity:total lung capacity and RV:TLC 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

Lung biopsy for histopathology by conventional thoracotomy or video-assisted thoracoscopy is sometimes the final step and is often necessary for a diagnosis. Biopsy yields a diagnosis in greater than 80% of patients. Because of the low diagnostic yield, transbronchial biopsies

are not recommended for the evaluation of ILD in children. Evaluation for possible systemic disease may also be necessary.

Molecular Diagnosis

For those genetic-based disorders, gene panels or whole exome sequencing may yield a rapid diagnosis (see Table 448.18).

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 for many forms of childhood ILD. 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 or 10-30 mg/kg of IV methylprednisolone given either weekly or for 3 consecutive days per month. Treatment length varies but is often initially given for 3-6 months with tapering of dosage dictated by clinical response. Alternative but not adequately evaluated agents include hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and IVIG. Investigational approaches involve specific agents directed against the action of cytokines, growth factors, or oxidants. In severe, progressive, or end-stage ILD, lung transplantation is an option, and outcomes are similar to other end-stage lung diseases in children. Appropriate treatment for underlying systemic disease or aspiration syndrome 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.

For those disorders with fibrotic ILD, antifibrotic therapy may be another option. The greatest experience with antifibrotic therapy has been in adults with IPF. Other indications for antifibrotic therapy include fibrosing ILD, autoimmune ILD, hypersensitivity pneumonitis, and nonspecific ILD. Nintedanib and pirfenidone have been approved for patients ≥ 18 years; both have demonstrated efficacy in slowing the decline in pulmonary function.

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 variable and depends on the specific diagnosis. Some children recover spontaneously without treatment, but other children steadily progress to death. Pulmonary hypertension and severe fibrosis are considered poor prognostic indicators.

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (ANTI-GBM DISEASE)

Anti-GBM disease, formerly known as Goodpasture disease, is the prototypical immunologic-mediated ILD (see Chapter 560.4). Because of the concurrent presentation of renal (glomerulonephritis) and pulmonary (alveolar hemorrhage) disease, the differential diagnosis focuses on distinguishing anti-GBM disease from vasculitis, infection, and other syndromes such as GPA, microscopic polyangiitis, Henoch-Schönlein purpura, and idiopathic pulmonary hemorrhage syndromes.

Pathophysiology

Immunology Factors

The development of anti-GBM antibodies against antigens that are present on the basement membranes of the glomerulus and alveolar 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.

Genetic Factors

Genetics appears to contribute strongly to the development of this disease, with the presence of MHC class II alleles DR15, DR4, DRB1*1501, DRB1*04, and DRB1*03 predisposing to disease. The disease is triggered by environmental factors in those with a genetic predisposition. There may be other genetic factors as well, and our understanding of the genetics involved in anti-GBM disease is evolving.

Environmental Factors

Exposure to cigarette smoke appears to be a strong factor in the development anti-GBM 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 nonsmokers who have anti-GBM disease. Other injuries to the alveoli from infection, hydrocarbon inhalation, or cocaine inhalation have been reported as associated events before the development of anti-GBM disease.

Clinical Manifestations

The majority of patients present with many days or weeks of cough, dyspnea, and fatigue, and up to 60% present with 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. 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 is positive in more than 90% of patients with anti-GBM disease. A complete blood count may 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 ANCA should also be performed and are positive in approximately 25–30% of patients concurrently with anti-GBM antibodies. The ANCA that is often positive is anti-myeloperoxidase ANCA.

Chest Radiography

Chest radiography in anti-GBM 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 of the chest reveals a diffuse ground-glass pattern or opacities.

Pulmonary Function Testing

Spirometry may be suggestive of a restrictive defect with reduction in FVC and FEV₁. 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 test takes advantage of hemoglobin's high affinity to bind carbon monoxide. Current data suggest that DLCO 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

Defining pulmonary hemorrhage can often be best assessed through bronchoscopy with BAL. The visual presence of blood during bronchoscopy will be obvious. Infections must be ruled out in many

cases. The cytology from the BAL may reveal hemosiderin-laden macrophages through Prussian blue staining. These macrophages would have engulfed and broken down the red blood cells, leaving iron in these cells.

Tissue Histopathology

The most common tissue obtained for diagnosis is a kidney biopsy. Kidney biopsies most commonly reveal crescentic glomerulonephritis with positive anti-GBM. Staining for IgG and complement is found by immunofluorescence along the basement membrane in a linear pattern. This antibody deposition pattern led to the investigation of endogenous antigens in the basement membrane. Although less likely to be performed in anti-GBM disease, 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.

Treatment

More than half of patients with anti-GBM disease who forego treatment die within 2 years from either respiratory failure, renal failure, or both. After a diagnosis is made, therapy with corticosteroids coupled with oral cyclophosphamide is initiated. The addition of daily plasmapheresis may accelerate improvement. Alternative therapies are rituximab or mycophenolate. Anti-GBM antibodies are monitored during treatment. Survival is affected by the need for ongoing dialysis. Kidney transplant is an option for those with significant renal impairment. Patients who do not require persistent dialysis have a survival rate at 1 year of 80% or more.

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448.6 Neuroendocrine Cell Hyperplasia of Infancy

W. Adam Gower

NEHI is an idiopathic form of diffuse lung disease that typically presents during the first year of life with persistent tachypnea, retractions, hypoxemia, crackles, and failure to thrive. Initial descriptions of NEHI used the term *persistent tachypnea of infancy*; some authors now use this to refer to both NEHI and pulmonary interstitial glycogenosis. Characteristic findings are seen on chest imaging studies and lung histopathology. Pulmonary function studies typically demonstrate an obstructive pattern with air trapping. *There are no effective specific therapies for NEHI, and the usual approach is supportive care.* The natural course is typically one of gradual improvement of symptoms, although exacerbations may occur throughout childhood, and potentially into adulthood. The long-term consequences of this disorder are not well-delineated.

EPIDEMIOLOGY

The prevalence of NEHI is not known, but it is generally considered to be a rare lung disease. Some studies have noted a slight male predominance. Otherwise, no other clear maternal or patient-level risk factors have been identified. Cases of NEHI have been reported in the literature from North and South America, Europe, Asia, and Australia.

PATHOPHYSIOLOGY

The primary clue to the pathophysiology of NEHI is increased numbers of neuroendocrine cells (NECs) in the airways of affected children. NECs are normally found in the airways, where they exist as both as individual cells and innervated clusters known as *neuroendocrine bodies* (NEBs), and secrete factors such as gastrin releasing peptide (GRP) and serotonin (5-HT). They are thought to be involved in local oxygen sensing and may transmit signals to other cells. Increases in NECs are seen in several respiratory disorders

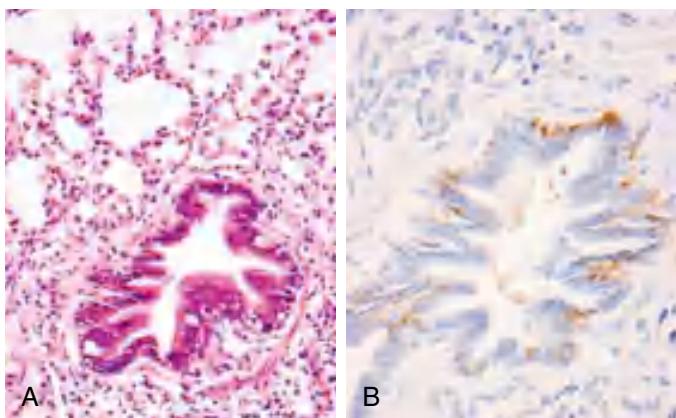


Fig. 448.12 Neuroendocrine cell hyperplasia of infancy. A, A small airway showing only minimal chronic inflammation on routine staining. B, Staining for bombesin shows increased numbers of neuroendocrine cells within the surface epithelium. (From Corrin B, Nicholson AG. *Pathology of the Lungs*, 3rd ed. Philadelphia: Churchill Livingstone; 2011: Fig. 2.19.)

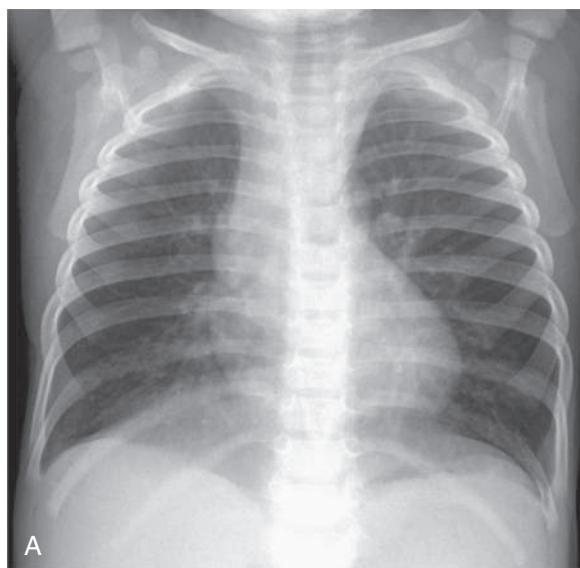


Fig. 448.13 A, Neuroendocrine cell hyperplasia of infancy in a 15-mo-old. Chest radiograph demonstrates pulmonary hyperinflation and parahilar opacities resembling reactive airways disease or bronchitis. B, Neuroendocrine cell hyperplasia of infancy. Axial expiratory CT image shows characteristic geographic ground-glass opacities involving the paramediastinal right middle lobe and lingula and the right lower lobe. (From Zucker EJ, Lee EY. Diffuse lung disease. In Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: Figs. 56.7 and 56.8, p. 541.)

of childhood, usually with other additional findings, where they are thought to be reactive to other primary pathology. It is unclear whether their presence in increased numbers in NEHI causes the clinical picture or is the result of abnormal pulmonary physiology secondary to some other primary factor. Increased numbers of NECs seem to be associated with increased small airway obstruction in those with NEHI.

Although most cases appear to be sporadic, familial NEHI has been described, suggesting a possible inherited mechanism and/or shared environmental factors between affected siblings. The association of NEHI with heterozygosity for a variant in the gene *Nkx2.1* has been described in one kindred. Variants in this gene are also known to cause a wide spectrum of disorders, including more severe forms of diffuse lung disease (see Chapter 448.5).

CLINICAL PRESENTATION

The symptoms of NEHI characteristically appear during infancy, although the diagnosis may be delayed until after the first year of life. The typical presentation includes persistent tachypnea, hypoxemia, retractions, and poor weight gain in an otherwise healthy infant. The exam reveals crackles or clear lung sounds, and cough, wheezing, and digital clubbing are not typical.

DIAGNOSIS

The diagnosis of NEHI requires that other more common causes of the presenting symptoms be ruled out. Strong consideration should be given to consultation with a pediatric pulmonologist when possible. Although children with NEHI may have comorbid GER and/or swallowing dysfunction, this is thought to be secondary to tachypnea and increased work of breathing rather than the cause of respiratory symptoms. Plain chest films may show hyperinflation. When biopsy material from the lung is stained with immunohistochemical reagents highlighting bombesin, increased numbers of positive-staining cells are noted in the airways. In general, biopsies from children with NEHI are remarkably void of fibrosis, inflammation, or signs of injury (Fig. 448.12).

Although the pattern of NEC hyperplasia seen in histopathology has classically been the gold standard for diagnosis of NEHI, HRCT of the chest has a high specificity, such that biopsy may be avoided in most cases. The classic pattern seen on chest CT is ground-glass opacities

in the lingula, right middle lobe, and perihilar regions, with air trapping on expiratory images. The lungs otherwise appear normal (Fig. 448.13). If a patient with clinically diagnosed NEHI has a more severe clinical course than expected, biopsy may be helpful to rule out other pathology.

The diagnosis of NEHI is supported by an obstructive pattern that does not reverse with bronchodilators, on either infant pulmonary function testing (iPFT) or standard spirometry. Static lung volumes may show air trapping with increased RV relative to the TLC. BAL findings are notable for lack of inflammatory markers, as compared to other pulmonary diseases of infancy.

Genetic testing may be useful to rule out disorders of surfactant metabolism and other causes of infant diffuse lung disease. Targeted testing for variants in *Nkx2.1* can be considered, but as this association has been found in only one kindred thus far, the diagnostic value of such testing is limited.

NATURAL COURSE AND TREATMENT

Because the symptoms of NEHI typically improve and eventually largely resolve over the first few years of life, the standard approach to treatment of NEHI is supportive. The time frame for clinical improvement in NEHI is variable. Symptoms with rest may improve, whereas those on exertion or with sleep persist. Affected children may require supplemental oxygen to maintain normal saturations, sometimes only with sleep or illnesses, but often at all times. Clinicians should have a low threshold to evaluate for sleep-related breathing disorders, and these should be treated accordingly. Inhaled or systemic corticosteroids are generally not thought to be helpful in treating the primary manifestations of NEHI.

Because they may expend more energy to breathe, children with NEHI may have difficulty gaining weight and often require supplemental nutrition. This may be delivered by gastrostomy tube. Management of GER and/or dysfunctional swallowing, when present, may be helpful. Mild abnormalities of the immune system may be seen in some patients with NEHI and, when present, may be addressed with specific therapy such as prophylactic antibiotics and/or immunoglobulin replacement.

When clinical symptoms improve, the need for supplemental oxygen and/or nutritional support typically decreases, and patients may be weaned as tolerated. Children with NEHI whose symptoms have improved may experience exacerbations later in childhood. These episodes may be associated with increased air trapping.

Although the symptoms of NEHI typically resolve during childhood, limited data suggest that some may persist into the adult years. This may manifest as exercise intolerance or an asthma-like picture. Obstruction with air trapping may be seen on PFT, and persistent abnormalities may be identified on chest imaging. No cases of respiratory failure, need for lung transplantation, or death caused by NEHI have been reported.

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448.7 Fibrotic Lung Disease

Deborah R. Liptzin, Jason P. Weinman, and Robin R. Deterding

Pulmonary fibrosis is scarring in the lung parenchyma (as opposed to bronchiectasis, which is scarring of the airways). Idiopathic pulmonary fibrosis is a common form of fibrotic lung disease in adults. This presents with usual interstitial pneumonia (a pathologic finding with patchy interstitial fibrosis, fibroblastic foci, and honeycomb change) (see Chapter 448.5). Additional adult fibrotic lung diseases include sarcoidosis, silicosis, coal worker's pneumoconiosis, and hypersensitivity pneumonitis (e.g., farmer's lung). In children, fibrotic lung disease is rare, and *idiopathic* pulmonary fibrosis has not been described. The differential diagnosis of *fibrotic* lung disease includes surfactant dysfunction pathogenic variants (see Chapter 444); immunocompromised patients with opportunistic infections, radiation-induced fibrosis, or status-post hematopoietic stem cell transplantation; patients with systemic disease processes that can lead to pulmonary fibrosis (systemic vasculitis, collagen vascular disease, juvenile idiopathic arthritis, storage diseases, Langerhans cell histiocytosis, sarcoidosis, systemic lupus erythematosus, systemic sclerosis, and nonspecific interstitial pneumonia); and pleuropulmonary fibroelastosis. Airway fibrosis can be seen in bronchiolitis obliterans (see Chapter 443.1) and aspiration (see Chapter 446) (Tables 448.20-448.22).

CLINICAL PRESENTATION

Pulmonary fibrosis classically presents with nonspecific respiratory symptoms such as cough, crackles, wheezes, prolonged expiratory phase, exercise intolerance, and hypoxemia, especially at nighttime.

Table 448.20 Diseases Associated with Pulmonary Fibrosis

- Idiopathic pulmonary fibrosis/nonspecific interstitial pneumonia
- Familial pulmonary fibrosis/familial interstitial pneumonia
- Hypersensitivity pneumonitis (many agents)
- Cryptogenic organizing pneumonia
- Adverse reaction to therapy (drugs, radiation)
- Pleuroparenchymal fibroelastosis
- Hermansky-Pudlak syndrome
- Sarcoidosis
- Eosinophilic pneumonia (primary or parasitic)
- Langerhans cell histiocytosis
- Dyskeratosis congenita
- Tuberous sclerosis
- Neurofibromatosis
- Erdheim-Chester disease
- Gaucher disease
- Niemann-Pick disease
- Familial hypocalciuric hypercalcemia
- Lysinuric protein intolerance
- IgG4-mediated immune disorder
- Myelodysplastic syndrome
- Progressive systemic sclerosis
- Other connective tissue diseases (SLE, dermatomyositis)
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis

Symptom onset can be insidious or rapid. In children, oxygen desaturation with activity may be the earliest sign of fibrotic lung disease, and cough, crackles, and wheezes may be later findings. Children with surfactant dysfunction pathogenic variants can present with respiratory failure in the neonatal period.

EVALUATION

Pulmonary function tests typically show restriction and reduced diffusion capacity. Air trapping can also be seen. Patients may desaturate with exercise challenges such as 6-minute walks, and this may be the first indication of disease in children.

There are a variety of findings on CT scan that suggest pulmonary fibrosis, and these findings can evolve over time. In surfactant dysfunction variants, ground-glass opacities are prominent early on with subsequent evolution to more typical findings of fibrosis such as reticular abnormalities, honeycombing, architectural distortion, and/or traction bronchiectasis. Typical findings in pediatric nonspecific interstitial pneumonia include subpleural sparing, ground-glass opacities, cystic change, reticular abnormalities, and bronchiectasis (Fig. 448.14). Novel measures of quantifying fibrosis have been described in the literature, and CT findings consistent with fibrosis are being used as criteria for study enrollment. Of note, CT findings and pulmonary function tests can be discrepant with stable pulmonary function tests over time, whereas the CT scan can evolve over the same period.

In certain disease processes such as surfactant deficiency (positive genetic testing) or genetic disorders of surfactant metabolism, biopsy is not necessary for diagnosis of fibrosis. Cryobiopsy is becoming popular in the adult pulmonary landscape but is in its infancy in the pediatric pulmonary field. In the absence of a definitive diagnosis, a thoracoscopic wedge biopsy is necessary for diagnosis and to guide treatment. Transbronchial biopsies in pediatrics are of limited utility because the small instruments typically obtain inadequate tissue specimens; transbronchial biopsies in pediatrics are limited to monitoring post-lung transplantation and for diagnosis of sarcoidosis. Pathologic findings in pulmonary fibrosis are variable, depending on the duration and etiology of disease (see Table 448.21), but typically include a component of interstitial inflammation, interstitial expansion by dense collagen, and lobular

Table 448.21 Pediatric Fibrotic Lung Diseases

DISEASES	CT FINDINGS	PATHOLOGY FINDINGS	ADDITIONAL EVALUATION	TREATMENT
Surfactant dysfunction	Early: Diffuse ground-glass opacities, septal thickening (crazy paving) Chronic: Decreased ground-glass opacities with reticulation and cystic lucencies	Variable: fibrosis, honeycomb cysts at end stage, NSIP, CPI, few globules of pulmonary alveolar proteinosis, foamy macrophages and cholesterol clefts (endogenous lipid pneumonia)	Genetic testing	Supportive care (nutrition, respiratory support, vaccinations), antifibrotic therapy <i>plus</i> hydroxychloroquine, azithromycin, high-dose intravenous steroids; genetic counseling
Aspiration	Acute: Consolidation and centrilobular (tree in bud) nodules with a dependent distribution Chronic: bronchiectasis, architectural distortion	Airway-centered lesions/ bronchiolitis, food particles with or without granulomas, foamy macrophages (endogenous lipid pneumonia), organizing pneumonia	Video fluoroscopic or fiberoptic endoscopic swallow evaluation	Stop aspiration through thickening feeds, gastric feeds, cleft repair
Radiation fibrosis	Architectural distortion, volume loss, traction bronchiectasis; often with geometric distribution related to radiation field	Pleural, septal, and paraseptal fibrosis; reactive atypia of alveolar epithelium and endothelium		Steroids may help
Bronchopulmonary dysplasia	Hyperlucent regions, cystic lucencies, architectural distortion (linear and subpleural triangular opacities)	Alveolar simplification and enlargement; patchy hyperinflation; interstitial fibrosis, with or without interlobular septal fibrosis	Consider evaluation for pulmonary hypertension and/or aspiration	Consider inhaled corticosteroids, inhaled steroids, diuretics
Nonspecific interstitial pneumonia (NSIP)	Basilar predominant findings of ground-glass opacities (often with subpleural sparing), reticulation, architectural distortion, and traction bronchiectasis	Interstitial lymphocytic inflammation and fibrosis with homogenous distribution		Consider steroids
Hypersensitivity pneumonitis (chronic)	Patchy and often parahilar reticulation, ground-glass opacities, centrilobular nodules; honeycombing (rare)	Airway-centered small noncaseating granulomas, multinucleated giant cells, lymphocytic bronchiolitis and peribronchiolitis, airway fibrosis, organizing pneumonia	Lymphocytosis in bronchoalveolar lavage, precipitins to specific antigen	Remove trigger, intravenous steroids
Autoimmune connective tissue disorders (collagen vascular disease)	See NSIP; honeycombing (rare)	NSIP; lymphoid hyperplasia; fibrosis and cystic change; pleuritis and pleural fibrosis (variable); chronic vasculopathy (variable); airway fibrosis (variable)	Serologic studies	Disease-specific immune modulation
Drug reactions	Peripheral predominant consolidation or ground glass opacities; reverse halo sign; see NSIP; honeycombing (rare)	Variable: organizing pneumonia, NSIP, UIP, DAD, pulmonary hemorrhage, eosinophilic pneumonia		Drug avoidance
Infection	Acute: Consolidation and centrilobular (tree in bud) nodules; appearance and distribution vary with type of infection Chronic: May progress to IPF/UIP with honeycombing	Acute: Neutrophilic alveolitis (bacterial) or lymphocytic bronchiolitis (viral) Chronic: Variable airway fibrosis (constrictive/obliterative bronchiolitis) and interstitial fibrosis		Antimicrobials
Immunodeficiency	Bronchiectasis, consolidation, centrilobular nodules	Follicular bronchiolitis or diffuse lymphoid hyperplasia; NSIP; LIP; GLILD	Immunologic and genetic testing	Treat underlying immunodeficiency
Usual interstitial pneumonia (UIP)	Honeycombing, reticulation, traction bronchiectasis, ground-glass opacities (less prominent than NSIP)	Fibroblast foci; interstitial, septal, and pleural fibrosis with heterogenous distribution; minimal to absent inflammation	Genetic testing	

Table 448.22 Genes Associated with Familial* or Idiopathic Pulmonary Fibrosis

GENE	GENE FUNCTION
IL1RN	Inhibitor of proinflammatory effect of IL-1 α and IL-1 β
IL8	Proinflammatory cytokine
FAM13A	Signal transduction
TLR3	Pathogen recognition and activation of innate immunity
TERT	Enzyme in telomerase complex maintaining telomere length
HLA-DRB1	Major histocompatibility complex—immune system
DSP	Tightly links adjacent cells
OBFC1	Stimulates the activity of DNA polymerase- α -primase
MUC5B	Influence on rheological properties of airway mucus, mucociliary transport, and airway defense
MUC2	Mucin production
TOLLIP	Regulator of innate immune responses mediated by toll-like receptor and the transforming growth factor β signaling pathway
ATP11A	Phospholipid translocation
MDGA2	Cell-cell interaction
MAPT	Promotes microtubule assembly and stability
SPPL2C	Protein cleavage
DPP9	Cell-cell adhesion
TGFB1	Set of peptides that controls proliferation, differentiation, and other functions in many cell types
SFTPC [†]	Component of surfactant fluid
SFTPA2 [†]	To modulate innate and adaptive immunity
ABCA3 [†]	Transport of lipids across plasma membrane
TERC [†]	Template in telomerase complex
DKC1 [†]	Stabilization of the template in telomerase complex
TINF2 [†]	Telomere maintenance
RTEL1 [†]	DNA helicase
PARN [†]	mRNA stability

*Also called familial interstitial pneumonia.

[†]Rarer variant.

Adapted from Kaur A, Mathai SK, Schwartz DA. Genetics in idiopathic pulmonary fibrosis pathogenesis, prognosis, and treatment. *Frontiers Med.* 2017;4:154, Tables 1 and 2.

remodeling (parenchymal architectural distortion and honeycomb cysts). Interlobular septal fibrosis, pleural fibrosis, and chronic pulmonary arteriopathy are common associated findings. Dense

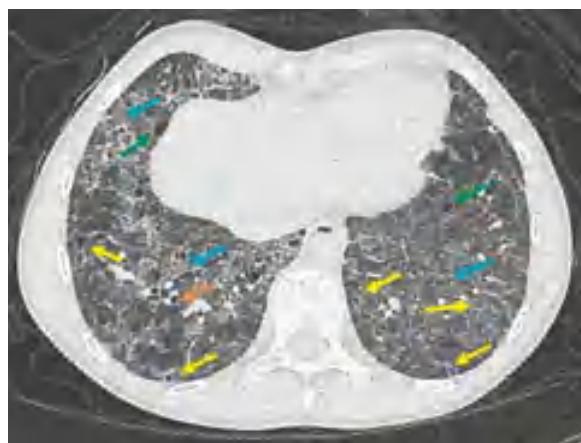


Fig. 448.14 Chest CT demonstrates typical CT findings in a pediatric patient with nonspecific interstitial pneumonia, including basilar-predominant ground-glass opacities (blue arrows), reticulation (yellow arrows), mild cystic change (green arrows), and bronchiectasis (orange arrow).

globules of pulmonary alveolar proteinosis material in infancy may indicate a genetic disorder of surfactant metabolism. Reactive lymphoid follicles suggest an immunologic process, such as autoimmune disease or immunodeficiency. Organizing pneumonia (polypoid aggregates of fibroblasts, *Masson bodies*) is a common feature in hypersensitivity pneumonitis and autoimmune diseases. The usual interstitial pneumonia pattern signaled by fibroblast foci arising within a background of dense interstitial fibrosis is almost never seen in children. Connective tissue stains, such as Masson trichrome, elastic Verhoff von Giesen, and Movat pentachrome, aid in determining the severity and distribution of collagen deposition.

TREATMENT

Treatment varies based on disease process (see Tables 448.20–448.22). Because of the nature of rare disease, treatment regimens are largely based on expert opinion, as controlled clinical trials are challenging to perform. *Antifibrotic agents approved in adults with fibrotic lung disease include pirfenidone and nintedanib, and weight-based dosing of nintedanib has been shown to have an acceptable safety profile in children.*

Monitoring may include evaluation of pulmonary function (spirometry, lung volumes, and diffusion capacity); functional evaluation of exercise (6-minute walk); and screening for comorbidities such as pulmonary hypertension, aspiration, poor weight gain, and sleep-associated breathing disorders. Respiratory support varies depending on each patient's needs, from no support to oxygen via nasal cannula and with ventilation (noninvasive or invasive); treatments may occur only with exercise and/or sleep or may be all the time. Comorbidities such as pulmonary hypertension or aspiration should be treated appropriately. Genetic counseling and recurrence risk should be provided with genetic forms of fibrotic lung disease. Patients should be counseled about preventing further lung damage from infection (up-to-date on vaccines, including pneumococcus, influenza, SARS-CoV-2, and respiratory syncytial virus) or particulate matter (air pollution, wildfires, wood-burning stoves, and environmental exposure to tobacco or marijuana).

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Chapter 449

Community-Acquired Pneumonia

Matthew S. Kelly and Thomas J. Sandora

Pneumonia, defined as inflammation of the lung parenchyma, is the leading infectious cause of death globally among children younger than 5 years, accounting for an estimated 880,000 deaths in 2015 (Fig. 449.1). Pneumonia mortality is closely linked to poverty; more than 99% of child pneumonia deaths are in low- and middle-income countries, with the highest pneumonia mortality rate occurring in Africa and South Asia.

In the United States, mortality from pneumonia in children declined by 97% between 1939 and 1996. This decline can largely be attributed to the development of antibiotics and vaccines and the expansion of medical insurance coverage for children. Effective vaccines against measles (see Chapter 293) and pertussis (see Chapter 243) contributed to the decline in child pneumonia mortality during the 20th century. *Haemophilus influenzae* type b (see Chapter 240) was also an important cause of bacterial pneumonia in young children but became uncommon after licensure of a conjugate vaccine in 1987. The introduction of pneumococcal conjugate vaccines (PCVs) (see Chapter 228) has been an important contributor to the further reductions in pneumonia mortality achieved over the past 2 decades. Epidemics (influenza, severe acute respiratory system coronavirus, Middle East respiratory syndrome, respiratory syncytial virus [RSV]) and pandemics (COVID-19) contribute to the incidence, morbidity, and mortality in pediatric patients with pneumonia. In addition, unexpected global increases in group A streptococcus (GAS) infections have contributed to both morbidity and mortality in children with pneumonia.

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 (see Chapter 448). The cause of pneumonia in an individual patient is often difficult to determine because direct sampling of lung tissue is invasive and rarely performed. Bacterial cultures of sputum or upper respiratory tract samples typically do not accurately reflect the cause of lower respiratory tract infection in children. *Streptococcus pneumoniae* (pneumococcus) is the most common bacterial pathogen in children 3 weeks to

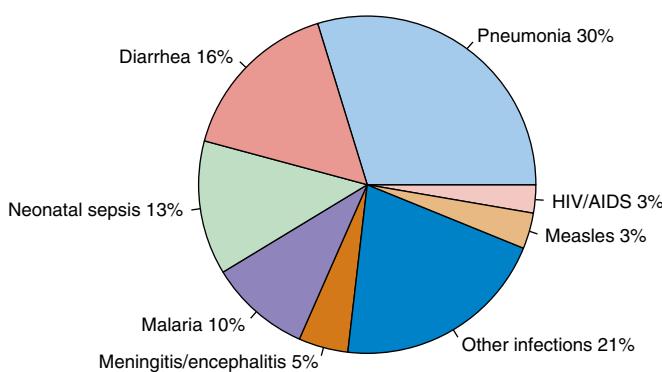


Fig. 449.1 Pneumonia is the leading infectious killer of children worldwide, as shown by this illustration of global distribution of cause-specific infectious mortality among children younger than age 5 yr in 2017. Pneumonia causes nearly one third of all under-5 deaths from infection. (From World Health Organization Global Health Observatory Data Repository, 2017 estimates.)

5 years of age, whereas *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are the most frequent bacterial pathogens in children 5 years and older. In addition to pneumococcus, other bacterial causes of pneumonia in previously healthy children in the United States include GAS (*Streptococcus pyogenes*; see Chapter 229) and *Staphylococcus aureus* (see Chapter 227.1) (Tables 449.1-449.3). *S. pneumoniae* or *S. aureus* pneumonia often complicates an illness caused by influenza viruses.

S. pneumoniae, *H. influenzae*, GAS, 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 261), nontuberculous mycobacteria (see Chapter 263), *Salmonella* (see Chapter 244), *Escherichia coli* (see Chapter 246), *Pneumocystis jirovecii* (see Chapter 290), and cytomegalovirus (see Chapter 302) should also 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 the most common causes of lower respiratory tract infections in infants and children older than 1 month but younger than 5 years of age (see Table 449.2). Viruses can be detected in 40–80% of children with pneumonia using molecular diagnostic methods (e.g., polymerase chain reaction [PCR]), with more than one respiratory virus identified in up to 20% of cases. Of the respiratory viruses, RSV (see Chapter 307) and rhinoviruses (see Chapter 310) are the most commonly identified pathogens, especially in children younger than 2 years of age. However, the role of rhinoviruses in severe lower respiratory tract infection remains unclear, as these viruses are frequently detected with co-infecting pathogens and among asymptomatic children. Other common viruses causing pneumonia include influenza viruses (see Chapter 305), human metapneumovirus (see Chapter 308), parainfluenza viruses (see Chapter 306), adenoviruses (see Chapter 309), enteroviruses (see Chapter 297), and coronaviruses (see Chapter 311), including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19; see Chapter 449.1).

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 viruses that occur each year. The typical pattern of these epidemics usually begins in the fall, when parainfluenza virus 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 viruses cause disease and excess hospitalization in all age groups. Knowledge of the prevailing viruses circulating in the community may lead to a presumptive initial diagnosis for children with acute respiratory illnesses.

Immunization status is relevant because children fully immunized against *H. influenzae* type b and *S. pneumoniae* are less likely to have pneumonia caused by these pathogens. Children who are immunocompromised or who have certain medical comorbidities may be at risk for specific pathogens, such as *Pseudomonas* spp. in patients with cystic fibrosis (see Chapter 454).

Pathogenesis

The lower respiratory tract possesses a number of defense mechanisms against infection, including mucociliary clearance, macrophages and secretory immunoglobulin A, and clearing of the airways by coughing. Previously, it was believed that the lower respiratory tract was—in the absence of infection—kept sterile by these mechanisms, supported primarily by culture-based studies. However, recent use of culture-independent techniques, including high-throughput sequencing methods, suggests that the lower respiratory tract contains diverse microbial communities. These data have challenged the traditional model of pneumonia pathogenesis that maintained that pneumonia was the result of invasion of the sterile lower respiratory tract by a single pathogen. More recent conceptual models postulate that pneumonia results from disruption of a complex lower respiratory ecosystem that is the

Table 449.1 Causes of Infectious Pneumonia

BACTERIAL	VIRAL
Common	Uncommon
<i>Streptococcus pneumoniae</i> Group B streptococcus Group A streptococcus <i>Staphylococcus aureus</i>	Consolidation, empyema Neonates Empyema Pneumatoceles, empyema; infants; nosocomial pneumonia
<i>Mycoplasma pneumoniae*</i>	Adolescents; summer to fall epidemics
<i>Chlamydophila pneumoniae*</i> <i>Chlamydia trachomatis</i> Mixed anaerobes Gram-negative enterics	Adolescents Infants Aspiration pneumonia Nosocomial pneumonia
Uncommon	FUNGAL
<i>Haemophilus influenzae</i> type b <i>Moraxella catarrhalis</i> <i>Neisseria meningitidis</i> <i>Francisella tularensis</i>	Unimmunized
<i>Nocardia</i> species <i>Chlamydophila psittaci*</i>	Animal, tick, fly contact; bioterrorism Immunocompromised patients Bird contact (especially parakeets)
<i>Yersinia pestis</i> (plague) <i>Legionella</i> species*	Rat contact; bioterrorism Exposure to contaminated water; nosocomial
<i>Coxiella burnetii*</i> (Q fever)	Animal (goat, sheep, cattle) exposure
VIRAL	RICKETTSIAL
Common	<i>Rickettsia rickettsiae</i>
Respiratory syncytial virus Parainfluenza types 1-4 Influenza A, B Adenovirus	Croup High fever; winter months Can be severe; often occurs between January and April
Human metapneumovirus	Similar to respiratory syncytial virus
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); COVID-19	Global pandemic
Uncommon	MYCOBACTERIAL
Rhinovirus Enterovirus D68, others	Rhinorrhea Neonates
	<i>Mycobacterium tuberculosis</i> <i>Mycobacterium avium</i> complex Other nontuberculous mycobacteria
	PARASITIC
	Various parasites (e.g., <i>Ascaris</i> , <i>Strongyloides</i> species)
	Eosinophilic pneumonia

*Atypical pneumonia syndrome; may have extrapulmonary manifestations, low-grade fever, patchy diffuse infiltrates, and poor response to β-lactam antibiotics.
Adapted from Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004: p. 29.

Table 449.2 Pneumonia Etiologies Grouped by Age of the Patient

AGE GROUP	FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)
Neonates (<3wk)	Group B streptococcus, <i>Escherichia coli</i> , other gram-negative bacilli, <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> (type b,* nontypeable)
3wk-3mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, human metapneumovirus, adenovirus), enterovirus D68, <i>S. pneumoniae</i> , <i>H. influenzae</i> (type b,* nontypeable); if patient is afebrile, consider <i>Chlamydia trachomatis</i>
4mo-4yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, human metapneumovirus, adenovirus), enterovirus D68, <i>S. pneumoniae</i> , <i>H. influenzae</i> (type b,* nontypeable), <i>Mycoplasma pneumoniae</i> , group A streptococcus
≥5yr	<i>M. pneumoniae</i> , <i>S. pneumoniae</i> , <i>Chlamydophila pneumoniae</i> , <i>H. influenzae</i> (type b,* nontypeable), influenza viruses, adenovirus, COVID-19, other respiratory viruses, <i>Legionella pneumophila</i>

**H. influenzae* type b is uncommon with routine immunization.

Adapted from Kliegman RM, Marcdante KJ, Jenson HJ, et al., eds. *Nelson Essentials of Pediatrics*, 5th ed. Philadelphia: Elsevier; 2006: p. 507.

site of dynamic interactions between potential pneumonia pathogens, resident microbial communities, and host immune defenses.

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 hypoxemia from ventilation-perfusion

Table 449.3 Pneumonia: Etiology Suggested by Exposure History	
EXPOSURE HISTORY	INFECTIOUS AGENT
Exposure to concurrent illness in school dormitory or household setting	<i>Neisseria meningitidis</i> , <i>Mycoplasma pneumoniae</i>
Exposure to persons with known or suspected COVID-19	SARS-CoV-2
ENVIRONMENTAL EXPOSURES	
Exposure to contaminated aerosols (e.g., air coolers, hospital water supply)	Legionnaires' disease
Exposure to goat hair, raw wool, animal hides	Anthrax
Ingestion of unpasteurized milk	Brucellosis
Exposure to bat droppings (caving) or dust from soil enriched with bird droppings	Histoplasmosis
Exposure to water contaminated with animal urine	Leptospirosis
Exposure to rodent droppings, urine, saliva	Hantavirus
Potential bioterrorism exposure	Anthrax, plague, tularemia
ZOONOTIC EXPOSURES	
Employment as abattoir work or veterinarian	Brucellosis
Exposure to cattle, goats, pigs	Anthrax, brucellosis
Exposure to ground squirrels, chipmunks, rabbits, prairie dogs, rats in Africa or southwestern United States	Plague
Hunting or exposure to rabbits, foxes, squirrels	Tularemia
Bites from flies or ticks	Tularemia
Exposure to birds (parrots, budgerigars, cockatoos, pigeons, turkeys)	Psittacosis
Exposure to infected dogs and cats	<i>Pasteurella multocida</i> , Q fever (<i>Coxiella burnetii</i>)
Exposure to infected goats, cattle, sheep, domestic animals, and their secretions (milk, amniotic fluid, placenta, feces)	Q fever (<i>C. burnetii</i>)
TRAVEL EXPOSURES	
Residence in or travel to San Joaquin Valley, southern California, southwestern Texas, southern Arizona, New Mexico	Coccidioidomycosis
Residence in or travel to Mississippi or Ohio river valleys, Great Lakes States, Caribbean, Central America, or Africa	Histoplasmosis, blastomycosis
Residence in or travel to southern China	Avian influenza
Residence in or travel to Arabian Peninsula	MERS-CoV
Residence in or travel to Southeast Asia	Paragonimiasis, melioidosis
Residence in or travel to West Indies, Australia, or Guam	Melioidosis

MERS-CoV, Middle East respiratory syndrome coronavirus; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. From Ellison RT III, Donowitz GR. Acute pneumonia. In: Bennett JE, Blaser MJ, Dolin R, et al., eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Saunders; 2015: Table 69.3, p. 828.

mismatch 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 disrupting the microbial communities that reside in the respiratory tract.

Bacterial pneumonia most often occurs when respiratory tract organisms colonize the upper respiratory tract and subsequently gain access to the lungs, but pneumonia may also result from direct seeding of lung tissue in the setting of bacteremia. When bacterial infection is established in the lung parenchyma, the pathologic process varies according to the invading organism. *M. pneumoniae* (see Chapter 269) attaches to the respiratory epithelium, inhibits ciliary action, and leads to cellular destruction and an inflammatory response in the submucosa. When the infection progresses, sloughed cellular debris, inflammatory cells, and mucus cause airway obstruction, with spread of infection occurring along the bronchial tree, as is seen in viral pneumonia. *S. pneumoniae* produces local edema that aids in the proliferation of organisms and their spread into adjacent portions of the lung, often resulting in the characteristic lobar consolidation. Lower respiratory tract infection caused by GAS typically results in more diffuse lung involvement 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 with frequent pleural involvement. *S. aureus* pneumonia manifests as confluent bronchopneumonia, which is often bilateral and characterized by the presence of extensive areas of hemorrhagic necrosis and irregular areas of cavitation of the lung parenchyma, resulting in pneumatoceles, empyema, and, at times, bronchopulmonary fistulas.

Recurrent pneumonia is defined as two or more episodes in a single year or three or more episodes ever, with radiographic clearing between occurrences. An underlying disorder should be considered if a child experiences recurrent pneumonia (Table 449.4).

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 manifested by intercostal, subcostal, and suprasternal retractions; nasal flaring; and use of accessory muscles is also 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 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. Lower lobe pneumonia may cause abdominal pain (but no tenderness), or the pain may be referred to the ipsilateral shoulder.

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. The liver may seem enlarged because of downward displacement of the diaphragm secondary to hyperinflation of the lungs or superimposed congestive heart failure.

Table 449.4 Differential Diagnosis of Recurrent Pneumonia	
HEREDITARY DISORDERS	
Cystic fibrosis	
Sickle cell disease	
DISORDERS OF IMMUNITY	
HIV/AIDS	
Bruton agammaglobulinemia	
Selective immunoglobulin G subclass deficiencies	
Common variable immunodeficiency syndrome	
Severe combined immunodeficiency syndrome	
Chronic granulomatous disease	
Hyperimmunoglobulin E syndromes	
Leukocyte adhesion defect	
DISORDERS OF CILIA	
Primary ciliary dyskinesia	
Kartagener syndrome	
ANATOMIC DISORDERS	
Pulmonary sequestration	
Lobar emphysema	
Congenital pulmonary airway malformation	
Gastroesophageal reflux	
Foreign body	
Tracheoesophageal fistula (H type)	
Bronchiectasis	
Aspiration (oropharyngeal incoordination)	
Aberrant bronchus	

Adapted from Kliegman RM, Marcdante KJ, Jenson HJ, et al., eds. *Nelson Essentials of Pediatrics*, 5th ed. Philadelphia: Elsevier; 2006: p. 507.

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 poor feeding, leading to the abrupt onset of fever, restlessness, apprehension, and respiratory distress. These infants typically 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. Auscultation 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 distension secondary to a paralytic ileus. Rapid progression of symptoms is characteristic in the most severe cases of bacterial pneumonia. Cyanosis often predicts multilobular involvement. Risk factors for severe pneumonia include temperature $>38.5^{\circ}\text{C}$, tachypnea, retractions, nasal flaring, grunting, capillary refill >2 seconds, cyanosis, tachycardia, and poor feeding.

DIAGNOSIS

In 2011, the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) published clinical practice guidelines for community-acquired pneumonia in children older than 3 months of age. These evidence-based guidelines provide recommendations for diagnostic testing and treatment of previously healthy children with pneumonia in both outpatient and inpatient settings. With the advent of advanced technologies and changing epidemiologic pathogens, these guidelines have required modifications.

An infiltrate on chest radiograph (posteroanterior and lateral views) supports the diagnosis of pneumonia; images may also identify a complication such as a pleural effusion or empyema. Viral pneumonia is usually characterized by hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing (Fig. 449.2). Confluent lobar consolidation is typically seen with pneumococcal pneumonia (Fig. 449.3). The radiographic appearance alone does not accurately identify

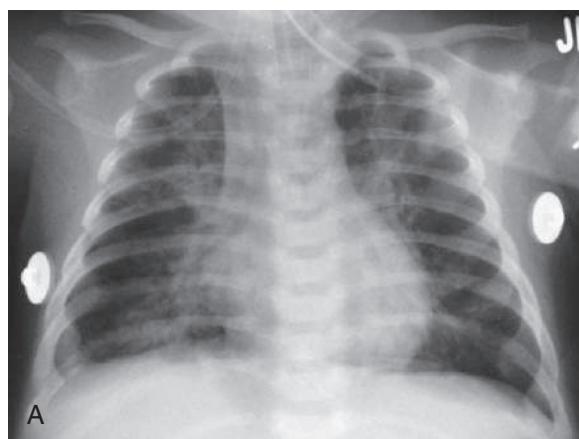


Fig. 449.2 A, Radiographic findings characteristic of respiratory syncytial virus pneumonia in a 6-mo-old infant with rapid respirations and fever. Anteroposterior radiograph of the chest shows hyperexpansion of the lungs with bilateral fine air space disease and streaks of density, indicating the presence of both pneumonia and atelectasis. An endotracheal tube is in place. B, One day later, the anteroposterior radiograph of the chest shows increased bilateral pneumonia.

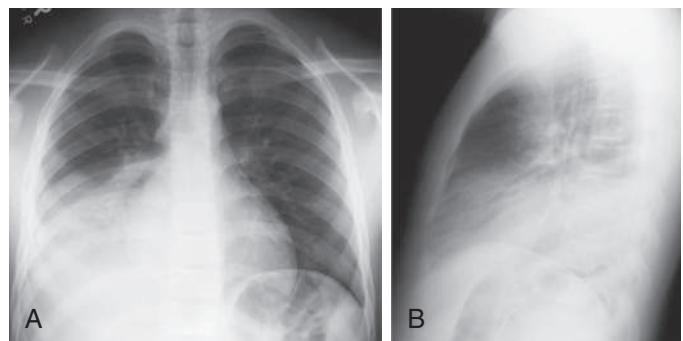


Fig. 449.3 Radiographic findings characteristic of pneumococcal pneumonia in a 14-yr-old male with cough and fever. Posteroanterior (A) and lateral (B) chest radiographs reveal consolidation in the right lower lobe, strongly suggesting bacterial pneumonia.

pneumonia etiology, and other clinical features of the illness must be considered. Repeat chest radiographs are not required for proof of cure for patients with uncomplicated pneumonia. Moreover, current PIDS-IDSA guidelines do not recommend that a chest radiograph be performed for children with suspected pneumonia (tachypnea, cough, fever, localized crackles, or decreased breath sounds) who are well enough to be managed as outpatients because imaging in this context only rarely changes management.

Point-of-care use of portable or handheld ultrasonography is highly sensitive and specific in diagnosing pneumonia in children by

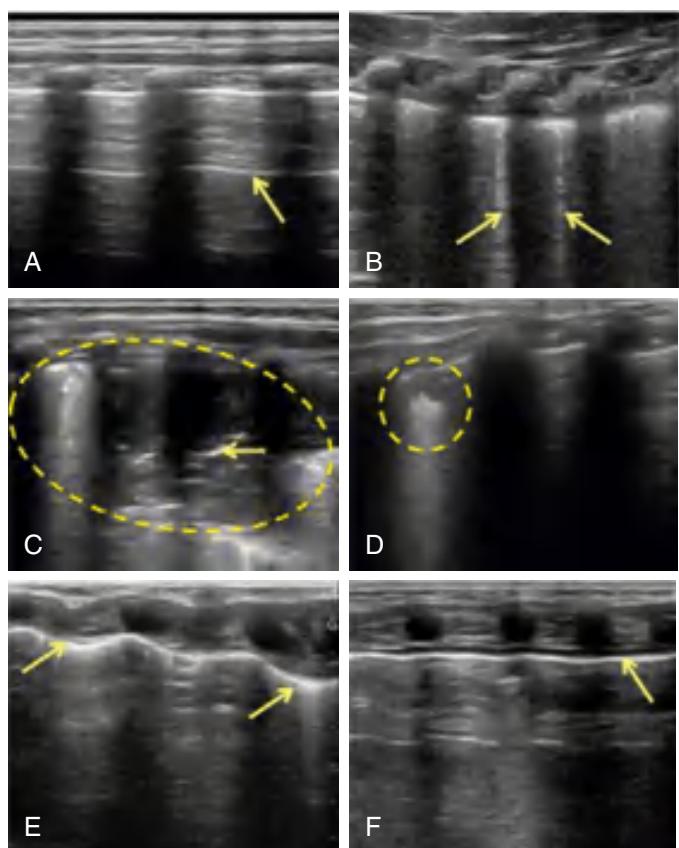


Fig. 449.4 Lung ultrasound patterns. A, Negative lung ultrasound pattern with A-line (arrow) and no other findings. Positive lung ultrasound patterns with (B) B-lines (arrows); (C) large consolidation (>1 cm) with tissue-like echo-texture (circle) and ultrasonographic bronchograms (arrow); (D) small consolidation (<1 cm; circle); (E) pleural line abnormality with thickening and irregularity (arrows); and (F) pleural effusion (arrow). (From Varshney T, Mok E, Shapiro AJ, et al. Point-of-care lung ultrasound in young children with respiratory tract infections and wheeze. *Emerg Med J.* 2016;33:603–610, Fig. 1.)

determining lung consolidations and air bronchograms or effusions (Fig. 449.4). However, the reliability of this imaging modality for pneumonia diagnosis is highly user-dependent, which has limited its widespread use.

The peripheral white blood cell (WBC) count can be useful in differentiating viral from bacterial pneumonia. In viral pneumonia, the WBC count can be normal or elevated but is usually not higher than $20,000/\text{mm}^3$, with a lymphocyte predominance. Bacterial pneumonia is often associated with an elevated WBC count, in the range of $15,000\text{--}40,000/\text{mm}^3$, and a predominance of polymorphonuclear leukocytes. 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; although pneumococcal pneumonia is associated with a higher WBC count, erythrocyte sedimentation rate, procalcitonin, and C-reactive protein level, there is considerable overlap.

The definitive diagnosis of a viral infection rests on the detection of the viral genome or antigen in respiratory tract secretions. Reliable PCR assays are widely available for the rapid detection of many respiratory viruses, including RSV, parainfluenza, influenza, human metapneumovirus, adenovirus, enterovirus, rhinovirus, and SARS-CoV-2. 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 virus. This diagnostic technique is laborious, slow, and not generally clinically useful because the infection usually has resolved by the time it is confirmed

Table 449.5 Factors Suggesting Need for Hospitalization of Children with Pneumonia

Age <6 mo
Immunocompromised state
Toxic appearance
Moderate to severe respiratory distress (retractions, nasal flaring, grunting)
Cyanosis/hypoxemia (oxygen saturation $<90\%$ breathing room air, sea level)
Shock (tachycardia, hypotension, prolonged capillary refill time)
Complicated pneumonia*
Sickle cell anemia with acute chest syndrome
Vomiting or inability to tolerate oral fluids or medications
Severe dehydration
No response to appropriate oral antibiotic therapy
Social factors (e.g., inability of caregivers to administer medications at home or follow up appropriately)
High-risk pathogen

*Pleural effusion, empyema, abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory distress syndrome, extrapulmonary infection (meningitis, arthritis, pericarditis, osteomyelitis, endocarditis), hemolytic uremic syndrome, or sepsis.

Adapted from Baltimore RS. Pneumonia. In: Jenson HB, Baltimore RS, eds. *Pediatric Infectious Diseases: Principles and Practice*. Philadelphia: WB Saunders; 2002: p. 801.

serologically. Serologic testing may be valuable as an epidemiologic tool to define the incidence and prevalence of various respiratory viral pathogens.

The definitive diagnosis of a typical 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, and percutaneous lung aspiration is invasive and not routinely performed. Blood culture is positive in only 10% of children with pneumococcal pneumonia (bacteremia is more common in GAS and *H. influenzae* pneumonias) and is not recommended for nontoxic-appearing children treated as outpatients. Blood cultures are recommended for children who fail to improve or have clinical deterioration, have complicated pneumonia (Table 449.5), or require hospitalization. Pertussis infection can be diagnosed by PCR or culture of a nasopharyngeal specimen; although culture is considered the gold standard for pertussis diagnosis, it is less sensitive than the available PCR assays. Acute infection caused by *M. pneumoniae* can be diagnosed on the basis of a PCR test result from a respiratory specimen or seroconversion in an immunoglobulin G assay. Cold agglutinins at titers $>1:64$ are also found in the blood of roughly half of patients with *M. pneumoniae* infections; however, cold agglutinins are nonspecific because other pathogens such as influenza viruses may also cause increases. Serologic evidence, such as antistreptolysin O and anti-DNase B titers, may also be useful in the diagnosis of GAS pneumonia.

Noninvasive diagnostic tests *may* help differentiate children with bacterial versus viral causes of pneumonia. Various biomarkers, including C-reactive protein, procalcitonin, and ESR, have been evaluated for their ability to differentiate these pneumonia etiologies. For many of these biomarkers, values differ in children with bacterial compared with viral causes of pneumonia (except adenovirus and influenza), but the reliability of these tests is not sufficiently high to justify routine clinical use. Cell-free next-generation sequencing of plasma or blood has been helpful in identifying pathogens in patients suspected of having bacterial pneumonia; identified pathogens include *S. pneumoniae*, *S. aureus*, and *Fusobacterium nucleatum* (blood cultures were negative in most of these patients). In addition, culture and PCR analysis of pleural fluid may also yield an organism.

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 (90 mg/kg/day orally divided twice daily) should be prescribed unless local data indicate a low prevalence of resistance.

Therapeutic alternatives include cefuroxime and amoxicillin/clavulanic acid. For school-age children and adolescents or when infection with *M. pneumoniae* or *C. pneumoniae* is suspected, a macrolide antibiotic is an appropriate choice for outpatient management. Azithromycin is generally preferred, but clarithromycin or doxycycline (for children 8 years or older) are alternatives. For adolescents, a respiratory fluoroquinolone (levofloxacin, moxifloxacin) may also be considered as an alternative if there are contraindications to other agents.

The empiric treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on local epidemiology, the immunization status of the child, and 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 ampicillin or penicillin G. For children who do not meet these criteria, ceftriaxone or cefotaxime may be used. If infection with *M. pneumoniae* or *C. pneumoniae* is suspected, a macrolide antibiotic should be included in the treatment regimen. If clinical features suggest staphylococcal pneumonia (pneumatoceles, empyema), initial antimicrobial therapy should also include vancomycin or clindamycin. For children with respiratory failure in the setting of influenza-methicillin-resistant *S. aureus* (MRSA) co-infection, data from a multicenter study support combination therapy with vancomycin and a second antibiotic with MRSA activity (e.g., clindamycin).

If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for preschool-age 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 449.5 notes the indications for admission to a hospital. Hospitalized children should receive supportive care and may require intravenous fluids; respiratory support, including supplemental oxygen, continuous positive airway pressure (CPAP), or mechanical ventilation; or vasoactive medications for hypotension or sepsis physiology.

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 hours. Several studies suggest that shorter courses (5–7 days) may also be effective, particularly for children managed on an outpatient basis. Available data do not support prolonged courses of treatment for uncomplicated pneumonia. Some studies suggest that a reduction of previously elevated serum procalcitonin levels to an absolute level (0.1–0.25 µg/L) may help determine when to stop treatment.

Despite substantial gains over the past 15 years, less than two thirds of children with symptoms of pneumonia are taken to an appropriate caregiver in low- and middle-income countries, and fewer than half receive antibiotics. The World Health Organization and other international groups have developed systems to train mothers and local healthcare providers in the recognition and appropriate antibiotic treatment of pneumonia. In addition to antibiotics, oral zinc (10 mg/day for <12 months, 20 mg/day for ≥12 months given for 7 days) may reduce mortality among children in low- and middle-income countries with clinically defined severe pneumonia. Bubble CPAP improves mortality from pneumonia with hypoxemia compared with standard oxygen therapy in settings without access to ventilator-derived CPAP or mechanical ventilation.

PROGNOSIS

Typically, patients with uncomplicated community-acquired bacterial pneumonia show response to therapy, with improvement in clinical symptoms (fever, cough, tachypnea, chest pain), within 48–72 hours 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 pleural effusion or empyema (see Table 449.5); (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; and (6) other noninfectious causes (including bronchiolitis obliterans, hypersensitivity pneumonitis, eosinophilic pneumonia, and granulomatosis with polyangiitis, formerly called *Wegener granulomatosis*). A chest radiograph is the first step in determining the reason for a lack of response to initial 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 countries 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 years 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 449.5) are usually the result of direct spread of bacterial infection within the thoracic cavity (pleural effusion, empyema, and pericarditis) or bacteremia and hematologic spread (Figs. 449.5–449.7). Meningitis, endocarditis, suppurative arthritis, and osteomyelitis are rare complications of hematologic spread of pneumococcal or *H. influenzae* type b infection.

S. aureus, *S. pneumoniae*, and *S. pyogenes* (GAS) are the most common causes of parapneumonic effusions and empyema. Nonetheless many effusions that complicate bacterial pneumonia are sterile. Analysis of pleural fluid parameters, including pH, glucose, protein, and lactate dehydrogenase, can differentiate transudative from exudative effusions (Table 449.6). However, current PIDS-IDSA guidelines do not recommend that these tests be performed because this distinction rarely changes management. Pleural fluid should be sent for Gram stain and bacterial culture, as this may identify the bacterial cause of pneumonia. Molecular methods, including bacterial species-specific PCR



Fig. 449.5 Chest radiograph of large right-sided pleural effusion complicating community-acquired pneumonia. (From de Benedictis FM, Kerem E, Chang AB, et al. Complicated pneumonia in children. Lancet. 2010;396:786–798, Fig. 1, p. 789.)

assays, detect pathogens and can often determine the bacterial etiology of the effusion if the culture is negative, particularly if the pleural fluid sample was obtained after initiation of antibiotics. A pleural fluid WBC count with differential may be helpful if there is suspicion for pulmonary tuberculosis or a noninfectious etiology for the pleural effusion, such as malignancy.

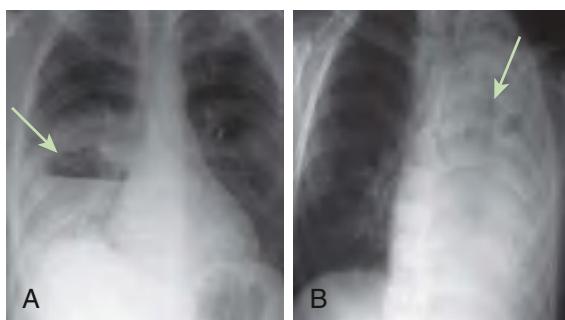


Fig. 449.6 Chest radiographs of lung abscess and necrotizing pneumonia. A, Lung abscess. A single thick walled, irregular cavity containing an air-fluid level can be seen (arrow). B, Necrotizing pneumonia. A completely opacified left hemithorax with multiple necrotic areas can be seen (arrow). (From de Benedictis FM, Kerem E, Chang AB, et al. Complicated pneumonia in children. Lancet. 2010;396:786–798, Fig. 2, p. 789.)

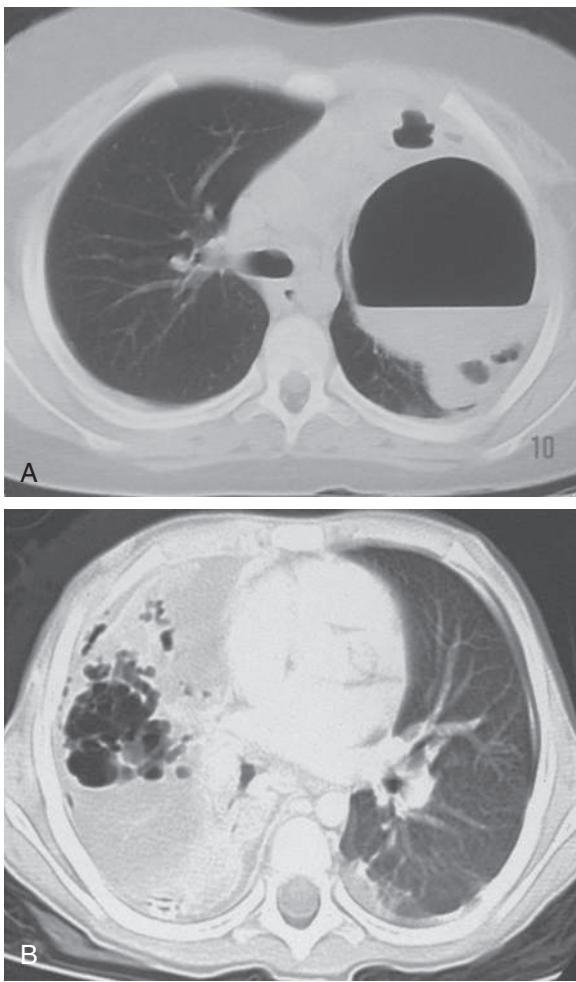


Fig. 449.7 Chest CT in complicated community-acquired pneumonia. A, Lung abscess. A large cavity containing an air-fluid level can be seen. B, Necrotizing pneumonia with cavitation. (From de Benedictis FM, Kerem E, Chang AB, et al. Complicated pneumonia in children. Lancet. 2010;396:786–798, Fig. 4, p. 790.)

Small (<1 cm on lateral decubitus radiograph), free-flowing para-pneumonic effusions often do not require drainage but respond to appropriate antibiotic therapy. Larger effusions should typically be drained, particularly if the effusion is purulent or associated with respiratory distress. Chest ultrasound, or alternatively CT, may be helpful in determining whether loculations are present. The mainstays of therapy include antibiotic therapy and drainage by tube thoracostomy with the instillation of fibrinolytic agents (tissue plasminogen activator). Video-assisted thoracoscopy is a less often employed alternative that enables debridement or lysis of adhesions and drainage of 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.

PREVENTION

The introduction of PCVs resulted in a substantial reduction in the incidence of pneumonia hospitalizations among children. The annual rate of all-cause pneumonia hospitalization among children younger than 2 years of age in the United States was 12.5 per 1,000 children during the period from 1997 to 1999. In 2000, seven-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. In 2010, 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States; data indicate that introduction of this vaccine resulted in a 16–27% further reduction in pneumonia hospitalizations among children relative to the post-PCV7 era.

Influenza vaccine may also prevent pneumonia hospitalizations among children and should be administered to all children >6 months of age. For infants <6 months of age, household contacts and other primary caregivers should receive the influenza vaccine. Maintaining high rates of vaccination for *H. influenzae* type b, pertussis, and measles remains important for the prevention of pneumonia from these causes. Several RSV vaccines are currently under development; introduction of an effective vaccine against RSV would be anticipated to substantially reduce pneumonia incidence among children, particularly young infants. Several vaccines that are highly effective in preventing COVID-19 have received Emergency Use Authorization by the U.S. Food and Drug Administration for use in children 6 months of age or older (see Chapter 449.1); such vaccines are often updated to cover emergence of new variants.

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449.1 COVID-19

Matthew S. Kelly and Thomas J. Sandora

See also Chapter 311.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of coronavirus disease 2019 (COVID-19), has created a global pandemic. As of July 2023, SARS-CoV-2 caused more than 767 million cases and 6.9 million deaths worldwide. SARS-CoV-2 is spread primarily through person-to-person respiratory transmission; viral particles in respiratory secretions that are released when an infected individual coughs, sneezes, or talks can infect another person when inhaled or through contact with mucous membranes. Direct person-to-person contact and fomites are believed to play minor roles in SARS-CoV-2 transmission. The incubation period for the virus can be up to 14 days after exposure, with most cases occurring within 4–5 days. Public health measures such as face masks, physical distancing, stay-at-home orders, and restrictions on public gatherings are highly effective in interrupting SARS-CoV-2 transmission (see Chapter 214). Several vaccines have been developed that are effective in preventing SARS-CoV-2 infection and severe COVID-19. SARS-CoV-2 has undergone substantial genetic evolution since it was first identified; several viral variants have emerged that are associated with different clinical symptoms along with increased transmissibility and reduced vaccine effectiveness.

Table 449.6 Features Differentiating Exudative from Transudative Pleural Effusion

FEATURE	TRANSUDATE	EXUDATE
Appearance	Serous	Cloudy
Leukocyte count	<10,000/mm ³	>50,000/mm ³
pH	>7.2	<7.2
Protein	<3.0 g/dL	>3.0 g/dL
Ratio of pleural fluid protein to serum	<0.5	>0.5
LDH	<200 IU/L	>200 IU/L
Ratio of pleural fluid LDH to serum	<0.6	>0.6
Glucose	≥60 mg/dL	<60 mg/dL

LDH, Lactate dehydrogenase.

From Septimus EJ. Pleural effusion and empyema. In: Bennett JE, Blaser MJ, Dolin R, et al. eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Saunders; 2015: Table 70-1, p. 851.

Some data suggest that children and adolescents may be less susceptible to SARS-CoV-2 infection than adults. In a meta-analysis that included data from 18 contact-tracing studies, children and adolescents less than 20 years of age had a 44% lower odds of being an infected contact compared to adults 20 years of age or older. However, widespread transmission of SARS-CoV-2 has occurred among children in schools and other congregate childcare settings, typically when face masks and other mitigation measures have not been in place.

CLINICAL MANIFESTATIONS

In children, COVID-19 is generally a mild illness, characterized most frequently by low-grade fever (30–50%) and cough (30–50%). Other commonly reported symptoms include nasal congestion or rhinorrhea, myalgias, and pharyngitis. Older children and adolescents often report headache, loss of smell (anosmia), or loss of taste (dysgeusia). Gastrointestinal symptoms such as abdominal pain, diarrhea, and vomiting occur less frequently but may be the presenting complaints in some children. Skin findings occur infrequently with SARS-CoV-2 infection, although maculopapular rash, urticarial lesions, and reddish-purple nodules on the toes (sometimes referred to as “COVID toes”) have been described. Tachypnea and signs of increased work of breathing should raise suspicion for pneumonia, the most common serious clinical manifestation of COVID-19. Severe neurologic symptoms such as seizures and encephalopathy have been reported among children hospitalized for severe COVID-19. *There are no signs or symptoms that can reliably distinguish COVID-19 from other illnesses caused by respiratory viruses or bacteria.* Up to 20–30% of children and adolescents with COVID-19 have asymptomatic infections; these individuals can still effectively transmit the virus to others.

Children and adolescents with SARS-CoV-2 infection are at a lower risk of severe COVID-19 than adults. Despite accounting for 10–20% of SARS-CoV-2 infections in the United States as of August 2021, children and adolescents represented less than 3% of hospitalizations and less than 0.5% of deaths from COVID-19. Children with underlying medical conditions are at higher risk of developing severe COVID-19. Data on risks associated with specific conditions in children are currently lacking, but the Centers for Disease Control and Prevention suggests that children with obesity, medical complexity, neurodevelopmental disorders, congenital heart disease, asthma or chronic lung disease, diabetes, or sickle cell disease may be at higher risk of progression to severe illness (Table 449.7). Children are also at higher risk of **multisystem inflammatory syndrome in children** (MIS-C; see Chapter 207), a postinfectious inflammatory condition that typically occurs in the 4–6 weeks after SARS-CoV-2 infection.

DIAGNOSIS

The IDSA recommends that children who have symptoms compatible with COVID-19, or asymptomatic individuals with known or suspected exposure to an individual diagnosed with COVID-19, be tested for SARS-CoV-2 using a nucleic acid amplification test (NAAT). In symptomatic individuals with a low clinical suspicion of COVID-19, a single NAAT test is considered sufficient, and testing should not be repeated if the result is negative. If the clinical suspicion for COVID-19 is considered intermediate or high but the initial test is negative, a repeat test should be performed 24–48 hours after initial testing. When available, standard laboratory-based NAATs or rapid reverse transcriptase (RT)-PCR tests are recommended over rapid isothermal NAATs because of higher sensitivity (98% for both standard laboratory-based NAATs and rapid RT-PCR vs 81% for rapid isothermal NAATs), despite comparable specificity. Rapid antigen tests are widely available and have high specificity but low to modest sensitivity compared with NAAT. Antigen test sensitivity is highly dependent on viral load, and therefore is influenced by the presence of symptoms and the timing of the test. For these reasons, IDSA does not recommend antigen tests as the preferred testing strategy, but rather maintains that antigen testing can identify some individuals infected with SARS-CoV-2 when molecular testing is not available.

A variety of specimen types can be tested for the presence of SARS-CoV-2, including nasopharyngeal (NP) swab, NP wash/aspirate, nasal wash/aspirate, oropharyngeal (OP) swab, nasal mid-turbinate (MT) swab, anterior nares (AN) swab, or saliva. Assay performance is highly dependent on collection procedure. IDSA recommends collecting an NP swab, MT swab, AN swab, saliva, or a combined AN/OP swab rather than an OP swab alone for symptomatic individuals suspected of having COVID-19. For hospitalized patients with suspected pneumonia and clinical suspicion for COVID-19, IDSA suggests a strategy of initially obtaining an upper respiratory specimen (e.g., NP swab) rather than a lower respiratory sample. However, if the initial specimen is negative and suspicion for disease remains high, a lower respiratory specimen (e.g., sputum, bronchoalveolar lavage fluid, or tracheal aspirate) should be collected rather than repeating the test from an upper respiratory sample.

Common laboratory abnormalities among children hospitalized for severe COVID-19 include lymphopenia, elevated aminotransaminases, and elevated markers of inflammation (e.g., C-reactive protein). Although imaging findings are neither sensitive nor specific for COVID-19, the most common abnormalities on chest radiography in children are perihilar bronchial wall thickening and/or air space consolidation. CT scans may show ground-glass opacities (mainly in the lower lobes) and/or air space consolidation. Chest radiography should be used as the first imaging modality to assess for pneumonia in symptomatic children, whereas CT should be reserved for assessing

Table 449.7 Framework for Assessing the Risk of Progression to Severe COVID-19 Based on Patient Conditions and COVID-19 Vaccination Status

CONDITIONS	RISK LEVEL BY VACCINATION STATUS ^a		
	UNVACCINATED	PRIMARY SERIES	UP TO DATE
STRONG OR CONSISTENT ASSOCIATION WITH PROGRESSION TO SEVERE COVID-19			
• Moderately or severely immunocompromised	High	High	High
• Obesity (BMI \geq 95th percentile for age), especially severe obesity (BMI \geq 120% of 95th percentile for age) ^b	High	Intermediate	Intermediate
• Medical complexity with dependence on respiratory technology ^c			
• Severe neurologic, genetic, metabolic, or other disability that results in impaired airway clearance or limitations in self-care or activities of daily living			
• Severe asthma or other severe chronic lung disease requiring \geq 2 inhaled or \geq 1 systemic medications daily			
• Severe congenital or acquired cardiac disease			
• Multiple moderate to severe chronic diseases			
MODERATE OR INCONSISTENT ASSOCIATION WITH PROGRESSION TO SEVERE COVID-19			
• Age <1 yr	Intermediate	Intermediate	Intermediate
• Prematurity in children age \leq 2 yr			
• Sickle cell disease			
• Diabetes mellitus (poorly controlled)			
• Nonsevere cardiac, neurologic, or metabolic disease ^d			
WEAK OR UNKNOWN ASSOCIATION WITH PROGRESSION TO SEVERE COVID-19			
• Mild asthma	Low	Low	Low
• Overweight			
• Diabetes mellitus (well controlled)			

^aUnvaccinated = individuals who are not eligible for COVID-19 vaccination or are <2 wk from the final dose of the primary series. Vaccinated with primary series = individuals who completed the primary series of two or three doses (the current CDC term is *fully vaccinated*) and are >2 wk after the final dose of the primary series but have not received a booster if they are eligible for a booster. Vaccinated and up to date = individuals who received the recommended primary series and booster doses.

^bThe degree of risk conferred by obesity in younger children is less clear than it is in older adolescents.

^cThis includes patients with a tracheostomy and those who require NIV.

^dThe data for this group are particularly limited.

BMI, Body mass index; CDC, Centers for Disease Control and Prevention; NIV, noninvasive ventilation; the Panel, the COVID-19 Treatment Guidelines Panel From NIH COVID-19 Treatment Guidelines (Table 3b). <https://www.covid19treatmentguidelines.nih.gov/tables/assessing-risk/>

for complications, particularly in children with coexisting medical conditions.

TREATMENT

For ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease (e.g., obesity or overweight, immunosuppression, medical-related technologic dependence, or a chronic medical condition such as kidney disease, diabetes, cardiovascular disease, sickle cell disease, or neurodevelopmental disorders), current treatment options include nirmatrelvir/ritonavir (\geq 12 years of age) or a 3-day course of remdesivir. Nirmatrelvir is an inhibitor of the main protease of SARS-CoV-2; coadministration with ritonavir results in higher concentrations and a longer half-life. Remdesivir is an antiviral agent that works by interfering with viral RNA transcription (see Table 449.8). As of July 2023, no monoclonal antibodies have been authorized for COVID-19 treatment or prophylaxis because of reduced susceptibility of circulating Omicron subvariants to these products.

For hospitalized children with severe illness ($\text{SpO}_2 \leq 94\%$ on room air, including patients on supplemental oxygen) or critical illness (mechanical ventilation or extracorporeal membrane oxygenation [ECMO]), dexamethasone treatment is recommended (Table 449.8). Inflammatory injury from the host immune response is thought to play a role in patients with severe or critical illness.

The IDSA recommends remdesivir for hospitalized patients with $\text{SpO}_2 \leq 94\%$ on room air, including patients on supplemental oxygen, but suggests against routine administration to patients on mechanical ventilation and/or ECMO. A panel of pediatric infectious diseases physicians and pharmacists recommended that remdesivir could be considered on a case-by-case basis for children with severe or critical COVID-19. Children receiving remdesivir should have daily measurements of creatinine and transaminases.

Tocilizumab is a monoclonal anti-interleukin (IL)-6-receptor blocking antibody. The IDSA suggests tocilizumab in addition to standard of care for hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic

inflammation. Baricitinib is a selective Janus kinase 1 and 2 inhibitor that has been studied as a substitute for dexamethasone in patients who cannot receive corticosteroids because of a contraindication (see Table 449.8).

PREVENTION

Vaccination is the most effective intervention to prevent COVID-19 infection and is highly protective against severe illness, hospitalization, and death. COVID-19 vaccination is available for use in children ≥ 6 months of age. Vaccine modifications are necessary when new variants emerge.

Because the emergence of viral variants with the potential to escape vaccine-induced immunity remains a threat, nonpharmaceutical

interventions to mitigate transmission of SARS-CoV-2 still play an important role in the public health response. Face mask use, eye protection, and physical distancing have all been demonstrated to reduce the risk of infection. A cross-sectional study conducted in the United States found an increase in reported mask-wearing was associated with an increased odds of transmission control. A modeling study by the Centers for Disease Control and Prevention demonstrated that high vaccination coverage and compliance with nonpharmaceutical interventions are essential to control COVID-19.

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Table 449.8 Therapeutic Management of Hospitalized Children with COVID-19

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized for COVID-19	For children age ≥ 12 yr admitted for COVID-19, use prophylactic anticoagulation unless contraindicated.
Does Not Require Supplemental Oxygen	For children admitted for COVID-19 who are at the highest risk of progression to severe COVID-19, ^a consider using remdesivir ^b for children age 12–17 yr. There is insufficient evidence for using remdesivir in children age 28 days to <12 yr. For children admitted for reasons other than COVID-19 who have mild to moderate COVID-19 and are at the highest risk of progression, see footnote a.
Requires Conventional Oxygen	Use one of the following options: • Remdesivir ^b • Dexamethasone plus remdesivir ^b for children with increasing oxygen needs, particularly adolescents
Requires Oxygen Through High-Flow Device or NIV ^d	Use one of the following options: • Dexamethasone • Dexamethasone plus remdesivir ^b For children who do not have rapid (e.g., within 24 hr) improvement in oxygenation after initiation of dexamethasone, baricitinib ^e or tocilizumab can be considered for children aged 12–17 yr (BIII) and for children age 2–11 yr, respectively.
Requires MV or ECMO ^f	Dexamethasone ^f For children who do not have rapid (e.g., within 24 hr) improvement in oxygenation after initiation of dexamethasone, baricitinib ^e or tocilizumab may be considered for children age 12–17 yr and for children age 2–11 yr, respectively.

^aFor example, for children who are severely immunocompromised regardless of COVID-19 vaccination status and those who are unvaccinated and have additional risk factors for progression.

^bThe clinical benefit of remdesivir is greatest if it is initiated within 10 days of symptom onset. Remdesivir should be given for 5 days or until hospital discharge, whichever comes first.

^cConventional oxygen refers to oxygen supplementation that is not high-flow oxygen, NIV, MV, or ECMO.

^dPatients who are receiving NIV or MV at baseline and require a substantial increase in baseline support should be treated per the recommendations for patients requiring new NIV or MV.

^eTofacitinib is an alternative if baricitinib is not available.

^fFor children who started receiving remdesivir before admission to the ICU, remdesivir should be continued to complete the treatment course.

ECMO, Extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; NIV, noninvasive ventilation.

From NIH COVID-19 Treatment Guidelines (Table 3c). <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-children/hospitalized-children-therapeutic-management/>

Chapter 450

E-Cigarette or Vaping Product Use–Associated Lung Injury (EVALI)

Lynn A. D'Andrea and Louella B. Amos

Beginning in 2019, there was a nationwide outbreak of patients who presented with acute lung injury believed to be related to vaping, designated as *E-cigarette or vaping product use–associated lung injury* (EVALI).

EPIDEMIOLOGY

As of January 2020, there were $>2,500$ hospitalized EVALI patients reported by all 50 states (approximately two thirds of patients were male). The median patient age was 21 years (range 13–85 years). The Centers for Disease Control and Prevention (CDC) stopped collecting data on EVALI cases in early 2020 because of the COVID-19 pandemic; although the number of cases may have decreased, EVALI must be considered in patients with features associated with the condition (Fig. 450.1).

Among hospitalized patients with information on substances used, $\sim 90\%$ reported using any tetrahydrocannabinol (THC)-containing product and $\sim 70\%$ reported using any nicotine-containing product; 40–60% reported both THC and nicotine use. The THC products were often flavored, prefilled THC cartridges obtained from black market sources.

PATHOPHYSIOLOGY

Carrier solvents or humectants such as propylene glycol and glycerin, as well as nicotine vapor itself, can cause airway inflammation

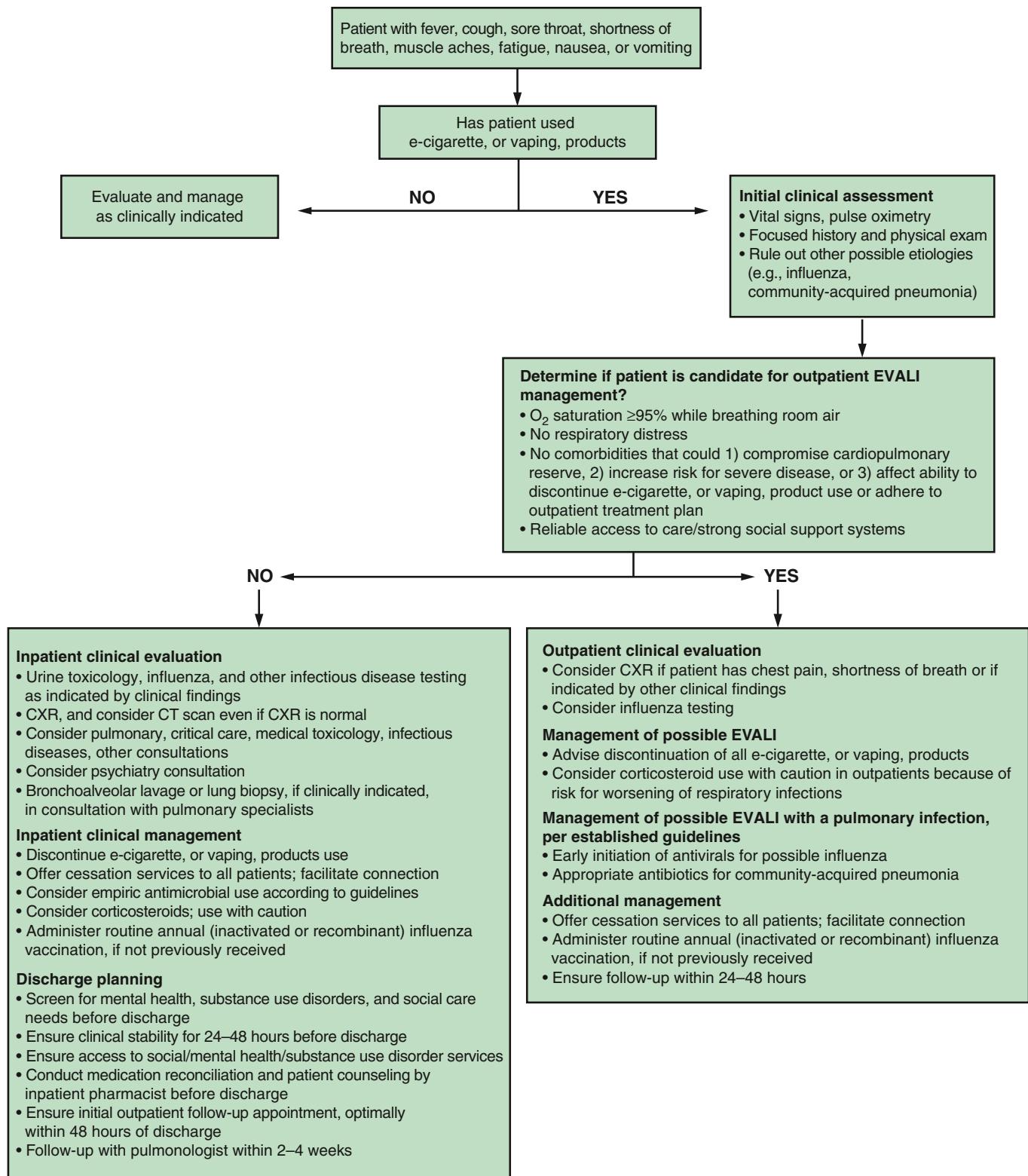


Fig. 450.1 Updated algorithm for management of patients with suspected e-cigarette, or vaping, product use-associated lung injury (EVALI), December 2019. CT, Computed tomography; CXR, chest x-ray.* Influenza vaccination recommendations: https://www.cdc.gov/mmwr/volumes/68/r1/rr6803a1.htm?s_cid=rr6803a1_w. (From Evans ME, Twentyman E, Click ES, et al. Update: interim guidance for health care professionals evaluating and caring for patients with suspected E-cigarette, or vaping, product use-associated lung injury and for reducing the risk of rehospitalization and death following hospital discharge – United States, December 2019. MMWR. 2020;68:1189–1194, Fig. p. 1191.)

that can induce airway remodeling and disrupt alveolar macrophage function. Flavoring additives generate by-products that directly injure airway epithelium. Vitamin E acetate that was used as a diluent in the THC-containing products disrupts alveolar macrophage

function and surfactant homeostasis. EVALI is best considered an airway-centered chemical pneumonitis rather than an exogenous lipid pneumonia. Thermal injury can also be a factor in acute lung injury.

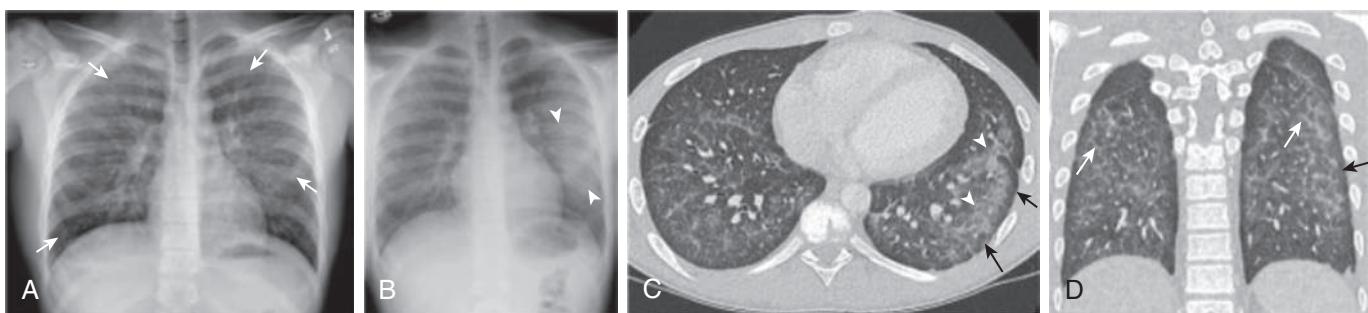


Fig. 450.2 E-cigarette, or vaping, product use–associated lung injury in a 16-yr-old male who presented with chest pain, shortness of breath, and cough for 1 month. **A**, Posteroanterior (PA) radiograph of the chest demonstrates faint nodular opacities in both lungs (arrows) with diffusely increased interstitial markings. **B**, PA radiograph of the chest obtained 2 days later demonstrates progression of the nodular opacities into confluent opacities in the left mid-lung (arrowheads). Axial (**C**) and coronal (**D**) chest CT images in lung windows (slice thickness 0.63 mm, kVp 100, mAs 61–106) obtained 4 days after the initial chest radiograph demonstrate centrilobular ground-glass nodules in both lungs and confluent ground-glass opacities in the left lower lobe (arrowheads) with subpleural sparing (black arrows) and interstitial septal thickening (white arrows). (From Thakrar PD, Boyd KP, Swanson CP, et al. E-cigarette, or vaping, product use–associated lung injury in adolescents: a review of imaging features. *Pediatr Radiol*. 2020;50:338–344, Fig. 1, p. 340.)

CLINICAL MANIFESTATIONS

Acutely, patients often present with a combination of respiratory distress, gastrointestinal (GI), and constitutional symptoms. Respiratory symptoms include shortness of breath, cough, hemoptysis, and chest or pleuritic pain. On physical examination, patients have tachypnea with hypoxemia and tachycardia. GI symptoms include nausea, vomiting, diarrhea, and abdominal pain.

Subacute constitutional and GI symptoms can occur day to weeks before the acute presentation. Constitutional symptoms include weight loss, fatigue, fever, myalgias, and chills.

DIAGNOSIS

There is no specific test for lung injury associated with EVALI; rather, evaluation should primarily focus on excluding infectious causes. It is important to evaluate for other possible causes (rheumatologic, neoplastic, cardiac) as appropriate (see Fig. 450.1).

Imaging

Chest radiographic evaluation is key in the diagnosis of EVALI, although findings are generally nonspecific (Fig. 450.2). Chest CT imaging is most consistent with acute lung injury from toxic inhalation, with centrilobular ground-glass opacities with subpleural sparing. The most common radiologic findings reported on chest x-ray are bilateral infiltrates, and ground-glass opacities predominantly at the bases. The most common radiologic findings reported on chest CT are bilateral infiltrates, bilateral ground-glass opacities, and subpleural sparing, followed by small pleural effusions and centrilobular nodularity. Pneumothorax and pneumomediastinum are less common.

Laboratory

Laboratory evaluation is suggestive of inflammation with neutrophilic leukocytosis, elevated C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Elevated transaminases (AST/ALT) and lactate dehydrogenase (LDH) have been reported in some patients. Urine drug screening is useful to confirm the presence of THC or nicotine.

Other Testing

Pulmonary Function Testing

The acute effects of EVALI on lung function are variable. In a case series of adolescents hospitalized with EVALI, predischarge testing demonstrated that >50% had an abnormality on spirometry, with a restrictive pattern occurring twice as often as obstruction; ~60% of patients had a decreased diffusion capacity, and ~50% had an abnormal 6-minute walk test. Patients continued to have abnormal testing at follow-up, including abnormal spirometry (both obstructive and restrictive patterns), decreased diffusion capacity, and rarely, 6-minute walk test. One follow-up study also identified abnormal 6-minute walk tests as a marker of lung injury and submaximal exercise capacity. However, another follow-up study showed ~85% of previously hospitalized pediatric patients had normal spirometry.

Bronchoscopy

Bronchoscopy with bronchoalveolar lavage is used to evaluate for possible infectious processes. Gross pathologic abnormalities can include mucosal hypervascularity, diffuse mucosal erythema, punctate mucosal hemorrhage, and frank airway bleeding consistent with a pulmonary hemorrhage. Cytopathologic findings commonly include lipid-laden macrophages on oil-red-O staining and elevated neutrophil counts more than 10% of total cell differential. Hemosiderin-laden macrophages are absent. Bacterial cultures are negative.

Caution is required when performing bronchoscopy with lavage, as it may worsen the patient's respiratory status. Many patients develop significant airway reactivity (bronchospasm) that requires intraprocedure management.

TREATMENT

Treatment focuses on supportive care. Supplemental oxygen may be required to maintain oxygen saturations in an appropriate range. Bronchodilators should be considered if there is an element of bronchospasm. Some patients have been treated with systemic corticosteroids with good improvement of their symptoms, but this should be considered on a case-by-case basis (see Fig. 450.1). Antibiotics should *only* be used for secondary infection.

Less often, patients have required more invasive respiratory support, including high-flow nasal cannula, mechanical ventilation, and rarely, extracorporeal membrane oxygenation (ECMO). There are rare case reports of patients requiring lung transplantation.

Follow-up should include recommendations regarding vaping cessation; some patients will require assistance with nicotine replacement therapy (see Chapter 157.2). Many adolescents require support from a mental health provider (see Fig. 450.1).

Advocacy and Prevention

In December 2019, the federal government passed legislation raising the age for purchasing tobacco products, including e-cigarettes, from 18 to 21 years. The FDA set the deadline for e-cigarette manufacturers to submit their marketing applications or risk having their products taken off the market. As of September 2021, the FDA ordered over 90% of e-cigarette products off the market; however, many products appealing to youth, including disposable flavored e-cigarettes, remain available, and the black market continues to thrive.

The initial EVALI outbreak primarily affected young adults, was driven by the use of THC-containing products from black market sources, and was strongly linked to vitamin E acetate. However, 15–20% of reported EVALI cases describe the exclusive use of nicotine-containing products. It is recommended that the term *EVALI* refer to all e-cigarette-related lung injuries, including other chronic respiratory symptoms of vaping (e.g., chronic wheeze, recurrent bronchitis, asthma exacerbations, emphysema).

Chapter 451

Pleurisy, Pleural Effusions, and Empyema

Aarthi P. Vemana and Suraiya K. Haider

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 449); other common causes include heart failure (see Chapter 491), rheumatologic and immune causes, and metastatic or intrathoracic malignancy. A variety of other diseases account for the remaining cases, including tuberculosis (see Chapter 261), lupus erythematosus (see Chapter 199), aspiration pneumonitis (see Chapter 446), uremia, pancreatitis, subdiaphragmatic abscess, and rheumatoid arthritis.

Inflammatory processes in the pleura are usually divided into three types: dry pleurisy, serofibrinous or serosanguineous, and purulent pleurisy or empyema.

451.1 Dry Pleurisy

Aarthi P. Vemana and Suraiya K. Haider

Dry pleurisy, formerly called *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 autoimmune and systemic inflammatory diseases such as systemic lupus erythematosus.

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, pleurisy can be caused by a severe delayed-type hypersensitivity reaction to *Mycobacterium 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 of pleurisy. 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

Dry pleurisy may be detected on radiographs as a diffuse haziness at the pleural surface or a dense, sharply demarcated shadow (Figs. 451.1 and 451.2). 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.

DIFFERENTIAL DIAGNOSIS

Pleurisy pain 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, gallbladder 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.

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451.2 Serofibrinous or Serosanguineous Pleurisy with Pleural Effusion

Aarthi P. Vemana and Suraiya K. Haider

Serofibrinous pleurisy is defined by a fibrinous exudate on the pleural surface and an exudative effusion of serous fluid into the pleural cavity. In general, 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, periarthritis, 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 fluid. Infectious etiologies include *Streptococcus pneumoniae*, *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA), group A streptococcus, and viral infections, including COVID-19 (although pleural disease is seen in approximately 10%).

PATHOGENESIS

Pleural fluid originates from the capillaries of the parietal pleura and is absorbed from the pleural space via pleural stoma 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, approximately 10 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 dry type, early signs and symptoms may be those of dry 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, retractions, tachypnea, orthopnea, or cyanosis. In children with bacterial pneumonia, pleural effusion should be suspected when symptoms do not improve after 48 hours of appropriate therapy.

Physical findings depend on the amount of effusion. Dullness to flatness 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

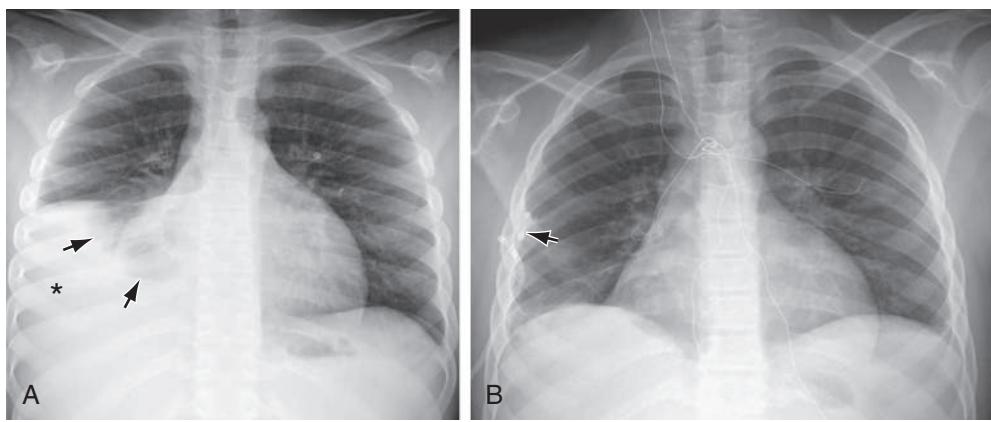


Fig. 451.1 A, Right pleural effusion (asterisk) caused by lupus erythematosus in a 12-yr-old child. Note compressed middle and lower lobes of the right lung (arrows). B, The effusion was evacuated, and the right lung was completely reexpanded after insertion of the pigtail chest tube (arrow).

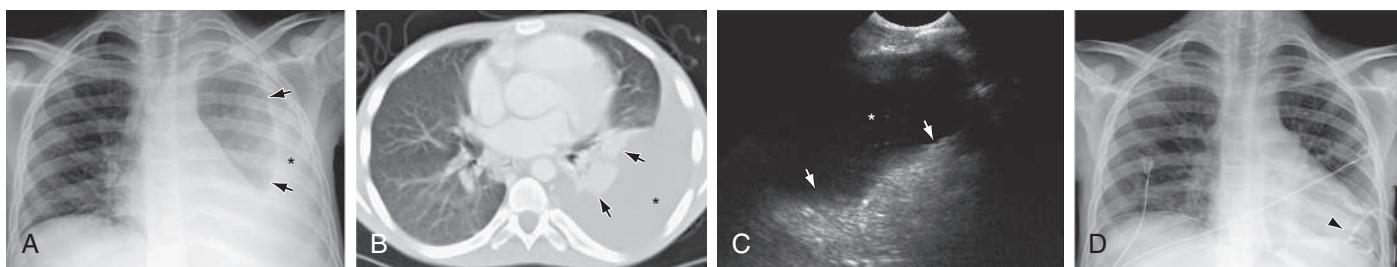


Fig. 451.2 Left pleural effusion in a teenager with AIDS and *Mycobacterium avium-intracellulare* infection. The pleural effusion (asterisk) is clearly seen on the chest radiograph (A), CT scan (B), and ultrasonogram (C) of the left chest. Arrows point to the compressed and atelectatic left lung. D, A pigtail chest tube (arrowhead) was inserted, resulting in reexpansion of the left lung.

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 homogeneous density obscuring the normal markings of the underlying lung, obliterating the costophrenic or cardiophrenic angles. Radiographs 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. Especially with large effusions, ultrasonography can identify the presence of septations, the lack of free movement of the fluid with gravity, and guide placement of a chest tube or site of thoracentesis located. Examination of the fluid is essential to differentiate **exudates** from **transudates** and to determine the type of exudate (see Table 449.6). Depending on the clinical scenario, pleural fluid is sent for culture for bacterial, fungal, and mycobacterial cultures; microbial analysis (quantitative polymerase chain reaction [qPCR], rapid antigen testing, and immunochromatography); Gram staining; and chemical evaluation of content, including protein, lactic dehydrogenase and glucose, amylase, specific gravity, total cell count and differential, cytologic examination for malignancy, and pH. Complete blood count and serum chemistry analysis should be obtained; hypoalbuminemia is often present. Exudates usually have at least one of the following features: protein level >3.0 g/dL, with pleural fluid:serum protein ratio >0.5 ; pleural fluid lactic dehydrogenase values >200 IU/L; or fluid:serum lactic dehydrogenase ratio >0.6 . Although systemic acidosis reduces the usefulness of pleural fluid pH measurements, pH <7.20 suggests an exudate. 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. Cytologic examination may reveal malignant cells, if present.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Unless the patient has a classic-appearing lobar pneumonia and the effusion is small, thoracentesis should be performed when pleural fluid is present or is suggested. Thoracentesis can differentiate serofibrinous pleurisy, empyema, hydrothorax, hemothorax, 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 hemothorax usually have fluid with a distinctive appearance, but differentiating serofibrinous from purulent pleurisy is impossible without microscopic examination of the fluid. 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. When the effusion is absorbed, adhesions often develop between the two 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

Treatment of the underlying pneumonia with antibiotics should be continued. If the effusion is less than 10 mm in size on a chest x-ray, there is no need for drainage. Drainage of large effusions can shorten the course of treatment and provide symptomatic relief. 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**. If sufficient fluid reaccumulates to cause tachypnea, chest tube drainage should be performed. In older children, 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 thick, loculated, or clearly purulent, chest tube drainage with fibrinolytic therapy or, less often, video-assisted thoracoscopic surgery (VATS) is indicated. 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. Monitoring with serial chest x-ray should be considered in children who have had complications or needed fibrinolytic treatment.

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451.3 Empyema

Aarthi P. Vemana and Suraiya K. Haider

Empyema is an accumulation of pus in the pleural space. It is most often associated with pneumonia (see Chapter 449) caused by gram-positive organisms such as *S. pneumoniae* (see Chapter 228), group A streptococcus, and *S. aureus* (see Chapter 227.1). The relative incidence of *Haemophilus influenzae* (see Chapter 240) empyema has decreased since the introduction of the *H. influenzae* type b vaccination. Gram-negative organisms, tuberculosis, fungi, viruses, and malignancy are less common causes. The disease can also be produced by rupture of a lung abscess into the pleural space, contamination introduced from trauma or thoracic surgery, or, rarely, mediastinitis or the extension of intraabdominal abscesses.

EPIDEMIOLOGY

Empyema is most frequently encountered in infants and preschool children. Although rates of bacterial pneumonia have decreased, the incidence of parapneumonic effusions has increased. This may be related to a shift toward more virulent organisms after the introduction of the 13-valent pneumococcal conjugate vaccine, with a trend toward serotypes not covered by the vaccine. Empyema occurs in 5–10% of children with bacterial pneumonia and in up to 86% of children with necrotizing pneumonia.

PATHOLOGY

Empyema has three 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 two 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. 451.3–451.5 and see Fig. 449.5). Ultrasonography, CT, and, less frequently, magnetic resonance imaging can all be used to further define the size of the effusion, identify septations, and assess

localizations. The maximal amount of fluid obtainable should be withdrawn by thoracentesis and studied (see Chapter 451.2). The effusion is an empyema if bacteria are present on Gram staining, the pH is <7.20, and there are >100,000 neutrophils/ μ L (see Chapter 449). Cultures of the fluid must always be performed to help identify the causal organism. Using standard culture methods, the organism can be identified in up to 60% of cases. The yield improves significantly with concomitant use of nucleic acid amplification techniques. Blood cultures may be positive and have a higher yield than cultures of the pleural fluid. Laboratory analysis shows leukocytosis and elevated erythrocyte sedimentation rate and elevated C-reactive protein.

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, thoracentesis, chest tube drainage, and use of a fibrinolytic agent; VATS and open decortication are used if there is poor resolution with the preceding therapies (see Chapter 461).

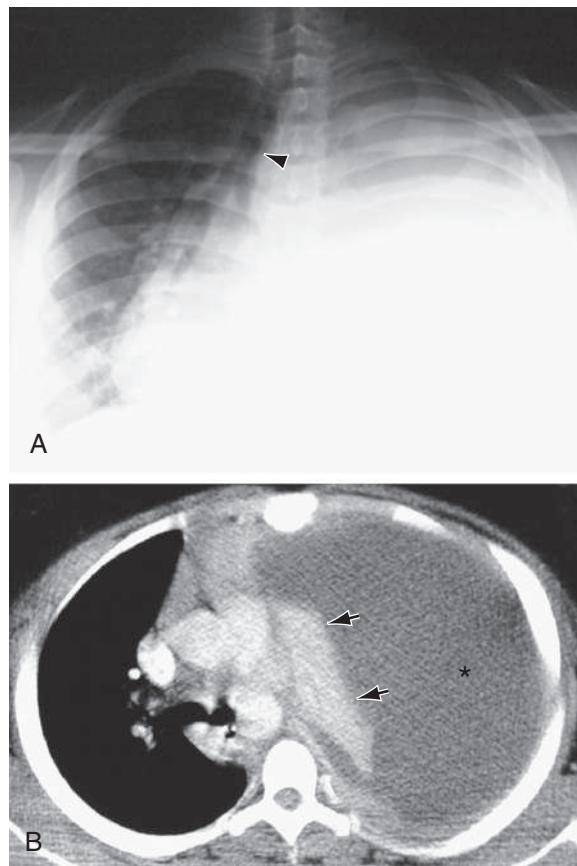


Fig. 451.3 Empyema and pneumonia in a teenager. A, Chest radiograph shows opacification of the left thorax. Note shift of mediastinum and trachea (arrowhead) to the right. B, Thoracic CT scan shows massive left pleural effusion (asterisk). Note the compression and atelectasis of the left lung (arrows) and shift of the mediastinum to the right.

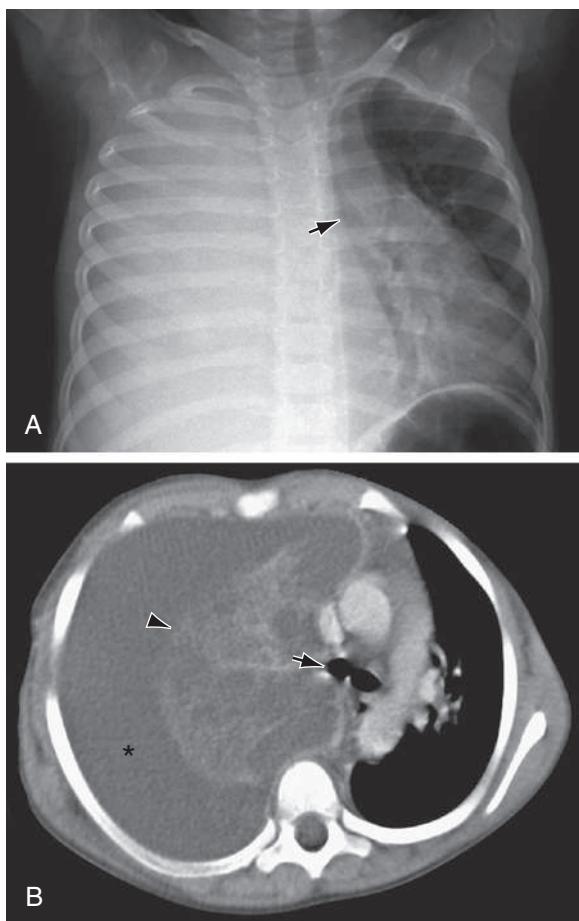


Fig. 451.4 Pneumonia and parapneumonic effusion in a 4-yr-old child. A, Chest radiograph shows complete opacification of the right thorax as a result of a large pleural effusion. Note the shift of the mediastinum and trachea (arrow) to the left. B, Thoracic CT scan shows a large right pleural effusion (asterisk) surrounding and compressing the consolidated right lung (arrowhead). Note the shift of the mediastinum and tracheal carina (arrow) to the left.

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 227, 228, and 240 for treatment of infections by *Staphylococcus*, *S. pneumoniae*, and *H. influenzae*, respectively. Treatment with systemic antibiotics is usually needed for 2-4 weeks, with the duration being guided by individual clinical response to treatment. Instillation of antibiotics into the pleural cavity does not improve results.

After empyema has been confirmed, interventions include closed chest tube drainage with fibrinolytics, decortication with VATS (video-assisted thoracoscopic surgery), and, less often, open thoracotomy. Multiple aspirations of the pleural cavity should not be attempted. Closed-chest tube drainage is controlled by an underwater seal or continuous suction; sometimes more than one 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 often promotes drainage, decreases the length of time a chest tube is in place, decreases fever, lessens the need for surgical intervention, and shortens hospitalization. The optimal fibrinolytic drug and dosages have not been determined. Streptokinase 15,000 units/kg in 50 mL of 0.9% saline, urokinase 40,000 units in 40 mL saline, and tissue plasminogen activator (tPA) 4 mg in 20-40 mL of saline have been used in the pediatric population. Although the combination of fibrinolytic therapy with dornase alfa (DNase) improves outcomes in adults with empyema, it has not been shown to consistently improve outcomes in pediatric patients with empyema. There is a risk of anaphylaxis with streptokinase, and all three drugs can be associated with hemorrhage and other complications.

If pneumatoceles form, no attempt should be made to treat them surgically or by aspiration, unless they reach sufficient size to cause respiratory compromise or become secondarily infected. Pneumatoceles usually resolve spontaneously with time. Extensive fibrinous changes may take place over the surface of the lungs owing to empyema, but they eventually resolve. 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.

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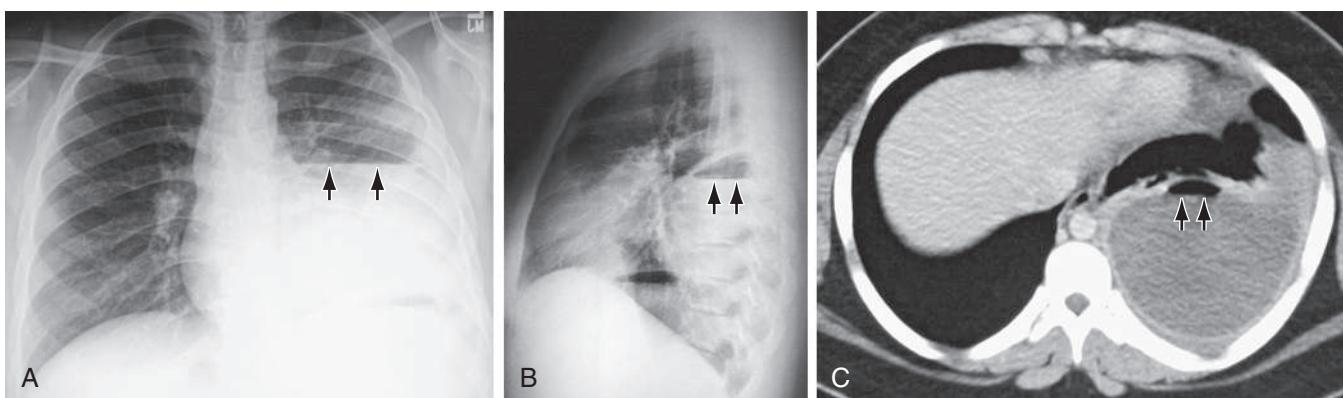


Fig. 451.5 Loculated hydropneumothorax. Frontal (A) and lateral (B) chest radiographs show loculated hydropneumothorax that complicated pneumonia in a 14-yr-old child. Arrows point to the horizontal air-fluid level at the interface between the intrapleural effusion and air. C, Thoracic CT scan helps to localize the loculated hydropneumothorax, with its air-fluid level (arrows).

Chapter 452

Bronchiectasis

Oren J. Lakser

Bronchiectasis is characterized by irreversible abnormal dilation and anatomic distortion of the bronchial tree and represents the common end stage of 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 (particularly in aboriginal children). Females are afflicted more frequently than males.

PATOPHYSIOLOGY AND PATHOGENESIS

In industrialized nations, cystic fibrosis (see Chapter 454) is the most common cause of clinically significant bronchiectasis. Other conditions associated with bronchiectasis include primary ciliary dyskinesia (see Chapter 455), postinfectious conditions, especially pertussis, measles, and tuberculosis, immune deficiency syndromes (especially humoral immunity), foreign body aspiration, and aspiration of gastric contents (Table 452.1). Bronchiectasis has also been associated with severe asthma in children. It can also be congenital, as in **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 **yellow nail syndrome** (pleural effusion, lymphedema, discolored nails) and **right middle lobe syndrome**. Right middle lobe syndrome is mostly associated with other generalized causes of bronchiectasis, including asthma, cystic fibrosis, primary ciliary dyskinesia, severe pneumonia, aspiration pneumonia, foreign bodies, and immune-deficient states.

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. More recently, nontypeable *Haemophilus influenzae* seems to be a common cause of infection in adults and children with bronchiectasis. *Streptococcus pneumoniae* and *Moraxella catarrhalis* are more common in children with bronchiectasis than in adult patients. **Chronic inflammation** similarly contributes to the mechanism by which obstruction leads to bronchiectasis. Both inadequate and exaggerated/dysregulated immune responses may play a role in the development of bronchiectasis. Activation of toll-like receptors results in the activation of nuclear factor κ B and the release of proinflammatory cytokines interleukin (IL)-1 β , 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 metalloproteinase (MMP)-8 and MMP-9. IL-6, IL-8, and tumor necrosis factor- α are elevated in the airways of patients with bronchiectasis. Eosinophils are also elevated in the airways of indigenous children with bronchiectasis, which promotes neutrophil recruitment, goblet cell hyperplasia, and airway destruction. There is an increase in proinflammatory cytotoxic T lymphocytes in the peripheral blood of children 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. This cycle results in a spectrum of pediatric suppurative lung disorders: protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD), and bronchiectasis. CSLD patients suffer from symptoms of bronchiectasis without its

radiographic features. In early stages, bronchiectasis consists primarily of bronchiolar wall thickening and destruction of elastin resulting in bronchial dilatation. In later stages, the bronchial walls develop cartilage destruction with associated pulmonary artery/arteriole vascular remodeling, resulting in pulmonary hypertension.

Bronchiectasis can manifest in any combination of three pathologic forms, best defined by high-resolution CT (HRCT) scan (Fig. 452.1). 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 **saccular** (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. 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), and **established bronchiectasis** (like the previous but with no resolution within 2 years). 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 chronic wet cough and/or production of copious purulent sputum. Younger children may swallow the sputum. In particular, wet or productive cough failing to respond to 4 weeks of oral antibiotics is predictive of the presence of chest CT-defined bronchiectasis. 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 and 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.

Table 452.1 Conditions That Predispose to Bronchiectasis in Children

PROXIMAL AIRWAY NARROWING

Airway wall compression (i.e., vascular ring, adenopathy impinging on airways)
Airway intraluminal obstruction (e.g., inhaled foreign body, granulation tissue)
Airway stenosis and malacia (tracheal, bronchial)

AIRWAY INJURY

Bronchiolitis obliterans (e.g., postviral, after lung transplantation)
Recurrent pneumonitis or pneumonia (e.g., pneumococcal pneumonia, aspiration pneumonia, tuberculosis, *B. pertussis*)

ALTERED PULMONARY HOST DEFENSES

Cystic fibrosis
Primary ciliary dyskinesia
Impaired cough (e.g., neuromuscular weakness conditions)

ALTERED IMMUNE STATES

Primary abnormalities (e.g., agammaglobulinemia, hypogammaglobulinemia, common variable immune deficiency, hyper IgE, hyper IgM, neutrophil dysfunction, gain-of-function STAT1 variants)
Secondary abnormalities (e.g., HIV infection, immunosuppressive agents)

OTHER

Systemic pseudohypoaldosteronism
Epithelial sodium channel variants (SCNN1A, SCNN1B)
Allergic bronchopulmonary aspergillosis
Plastic bronchitis
Right middle lobe syndrome

From Redding GJ. Bronchiectasis in children. *Pediatr Clin North Am*. 2009;56:157–171, Box 1.

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 the unaffected lung may be seen. Thin-section

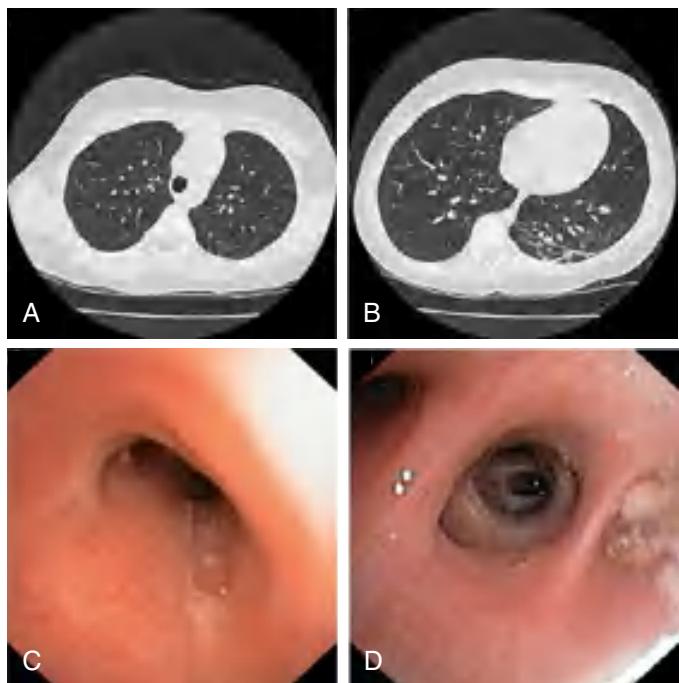


Fig. 452.1 High-resolution chest CT scans (A and B) and bronchoscopy images (C and D) in a child with bronchiectasis. (C and D) Bronchoscopy findings. Images from a chest high-resolution computed tomography (cHRCT) scan (A and B) in a 10-yr-old girl who presented with a chronic wet cough. The child was treated with a 2-wk course of IV antibiotics (after failing oral antibiotic treatment). The scan was reported as having no evidence of bronchiectasis by pediatric radiologists. At bronchoscopy thick mucus was seen in the trachea (C) and the right lower lobe (D). The case highlights the need to consider the diagnosis of bronchiectasis on the basis of history, examination findings, and using the pediatric cutoff (bronchoarterial ratio >0.8) for defining bronchiectasis on the cHRCT scan. (From Goyal V, Grimwood K, Marchant J, et al. Pediatric bronchiectasis: no longer an orphan disease. *Pediatr Pulmonol*. 2016;51:450–469.)

HRCT scanning and multidetector CT scanning are the gold standards because they have excellent sensitivity and specificity. CT provides further information on disease location, presence of mediastinal lesions, and the extent of segmental involvement. The main features of bronchiectasis in CT scans include (1) increased bronchoarterial ratio and *signet-ring* appearance; (2) bronchial wall thickening; (3) mucous plugging; (4) lack of bronchial tapering to the lung periphery—“tramlines”; (5) bronchial structures in the lung periphery; and (6) air trapping (mosaic perfusion), most obvious on expiration. The lower lobes (left $>$ right) are more commonly affected. Early in the course, tree-in-bud appearance can also be seen. These CT findings are used to define the bronchiectasis as *cylindrical* (“tram lines,” “signet ring appearance”), *varicose* (bronchi with “beaded contour”), *cystic* (cysts in “strings and clusters”), or mixed forms (Fig. 452.2).

TREATMENT

The initial therapy for patients with bronchiectasis is medical and aims at decreasing airway obstruction and controlling infection. Airway clearance techniques (e.g., gravity-assisted drainage, active cycle of breathing, positive expiratory pressure [PEP], acapella, high-frequency chest wall oscillation), antibiotics, and bronchodilators are essential. Two to four weeks of parenteral antibiotics (in hospital or at home) is often necessary to manage more severe acute exacerbations adequately. Exacerbations can be defined as the presence of one major criteria (wet cough enduring longer than 72 hours, increased cough frequency over 72 hours) plus one laboratory criteria (C-reactive protein >3 mg/L, serum IL-6 >2 ng/L, serum amyloid A >5 mg/L, elevated neutrophil percentage), two major criteria, or one major criterion plus two minor criteria (change in sputum color, breathlessness, chest pain, crackles/crepitations, wheeze). The presence of dyspnea (increased work of breathing) and/or hypoxemia should be considered a severe exacerbation, irrespective of duration.

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 *H. influenzae* non-type b, *S. pneumoniae*, *M. catarrhalis*, *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Viruses (most commonly human rhinovirus) are often found in children with bronchiectasis suffering from an exacerbation. A 14-day course of amoxicillin/clavulanic acid (22.5 mg/kg/dose twice daily) has been particularly successful at treating most pulmonary exacerbations. Azithromycin (5 mg/kg/day) is a reasonable alternative in those with penicillin allergy. For those experiencing frequent exacerbations of more than three per year, long-term prophylactic macrolide antibiotics (which also have immunomodulatory and antiinflammatory properties) or nebulized antibiotics (e.g., tobramycin, colistin, aztreonam, ciprofloxacin) may be beneficial (reduced exacerbations and hospitalizations, improved lung function) but may also increase antibiotic

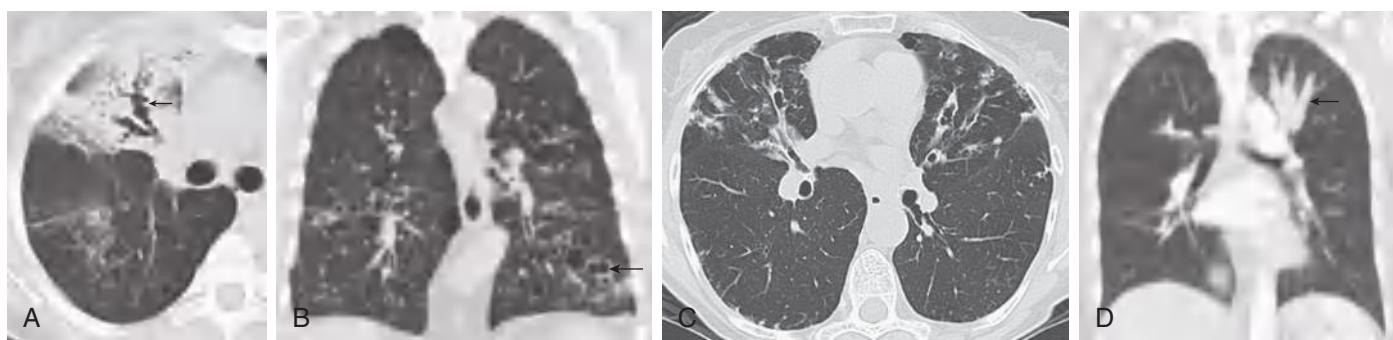


Fig. 452.2 Bronchiectasis. A, Axial CT image demonstrates a beaded appearance of dilated bronchi (arrow) in the right upper lobe, consistent with varicoid bronchiectasis. B, Coronal reformation CT image shows multiple foci of cystic bronchiectasis, with a few air-fluid levels (arrow). Also note paraseptal emphysema, most marked at the right apex. C, Bronchiectatic form of chronic atypical mycobacterial infection. Axial CT scan shows extensive bronchiectasis, bronchial wall thickening, and centrilobular nodules, most severe in the middle lobe and lingula. D, Allergic bronchopulmonary aspergillosis. Coronal reformation CT image demonstrates impacted bronchi in the left upper lobe (arrow) producing a “gloved finger” appearance. (From Boiselle PM. Airway. In: Haaga JR, Boll DT, eds. *CT and MRI of the Whole Body*, 6th ed. Philadelphia: Elsevier; 2017: Figs 40-30, 32-34.)

resistance. Airway hydration (inhaled hypertonic saline or mannitol) also improves quality of life in adults with bronchiectasis, but there are few studies in children. 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 and may improve growth and reduce the need for intravenous antibiotics. Lung transplantation can also be performed in patients with bronchiectasis. There is no 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. Preventive strategies, including immunization against typical respiratory pathogens (influenza, pneumococci), are generally recommended.

Development of novel treatments is ongoing and centered around targeting three components of the vicious cycle of bronchiectasis: bacterial infection (vitamin D supplementation, exogenous granulocyte-macrophage stimulating factor, phosphodiesterase 4 inhibitors, statins), neutrophilic inflammation (e.g., neutrophil elastase inhibitors, cathepsin C inhibitors, CXCR2 receptor antagonists), and mucociliary clearance (epithelial sodium channel inhibitors).

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. In some children and adolescents, their bronchiectasis is reversible and/or preventable. Factors important for reversibility and/or prevention of bronchiectasis include early identification and treatment of inhaled foreign bodies, preventing early and severe pneumonia, preventing recurrent protracted bacterial bronchitis, treating primary immunodeficiency disorders causing bronchiectasis, promoting breastfeeding and immunization, and avoiding tobacco smoke and other pollutants.

Thus earlier recognition or prevention of predisposing conditions, specialist multidisciplinary management, more powerful and broad-spectrum antibiotics, and improved surgical outcomes will further improve the prognosis for children with bronchiectasis.

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Chapter 453

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 *pulmonary 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) and result in less morbidity than in adults.

PATHOLOGY AND PATHOGENESIS

Multiple conditions predispose children to the development of pulmonary abscesses, including aspiration, pneumonia, cystic fibrosis (see Chapter 454), gastroesophageal reflux (see Chapter 369), tracheoesophageal fistula (see Chapter 365.1), immunodeficiencies, postoperative complications of tonsillectomy and adenoidectomy, seizures,

a variety of neurologic diseases, and other conditions associated with impaired mucociliary defense. Lung abscesses have been associated with e-cigarette or vaping product use-associated lung injury (EVALI; see Chapter 450). 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 angiosus*, group A streptococcus, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and very rarely, *Mycoplasma pneumoniae*. Aerobic and anaerobic cultures should be part of the workup 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 fever, cough, and emesis. Other common symptoms include tachypnea, dyspnea, chest pain, 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. 453.1). A chest CT scan can provide better anatomic definition of an abscess, including location and size (Fig. 453.2). Ultrasound can also help provide rapid diagnosis and procedural guidance.

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. 453.3). Pneumatoceles often resolve spontaneously with the treatment of the specific cause of the pneumonia. The differential diagnosis of a cavitary lung lesion is noted in Table 453.1.

The determination of the etiologic bacteria in a lung abscess can be 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.

TREATMENT

Conservative management is recommended for pulmonary abscess. Most experts advocate a 2- to 3-week course of parenteral antibiotics

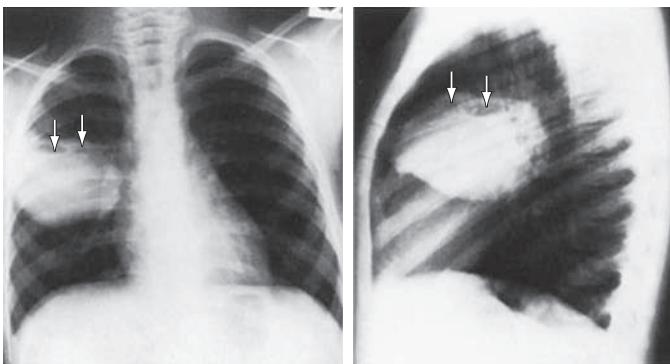


Fig. 453.1 Multiloculated lung abscess (arrows). (From Brook I. Lung abscess and pulmonary infections due to anaerobic bacteria. In Chernick V, Boat TF, Wilmott RW, et al., eds. *Kendig's Disorders of the Respiratory Tract in Children*, 7th ed. Philadelphia: WB Saunders; 2006:482.)

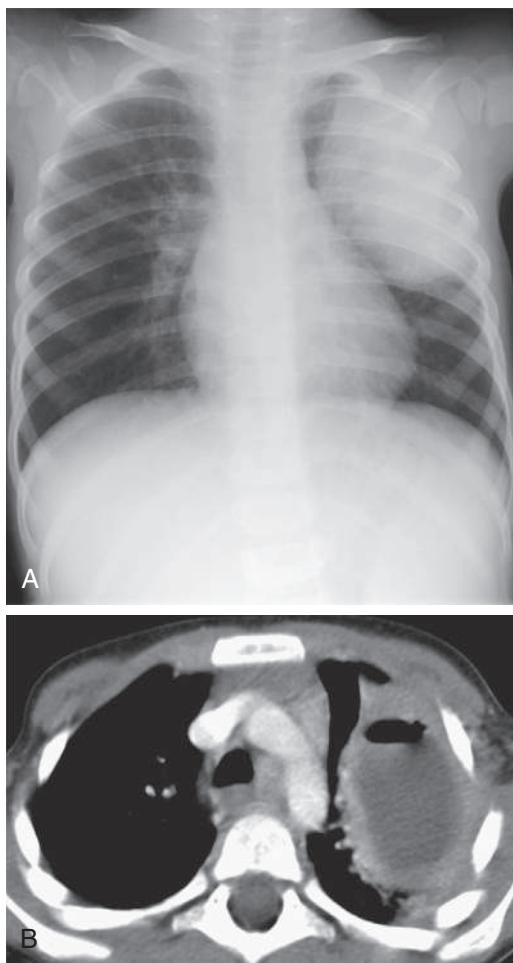


Fig. 453.2 Pulmonary abscess in a 2-yr-old male with persistent cough. A, Chest radiograph shows large oval mass in the left upper lobe. B, CT scan demonstrates an abscess with a thick enhancing wall that contains both air and fluid. (From Slovis T, ed. *Caffey's Pediatric Diagnostic Imaging*, 11th ed. Philadelphia: Mosby; 2008, Fig. 78-3, p. 1297.)

for uncomplicated cases, followed by a course of oral antibiotics to complete a total of 3-4 weeks. Antibiotic choice should be guided by results of Gram stain and culture but initially should include agents with aerobic and anaerobic coverage. Treatment regimens should include a penicillinase-resistant agent active against *S. aureus* and anaerobic coverage, typically with clindamycin or ampicillin-sulbactam. If gram-negative

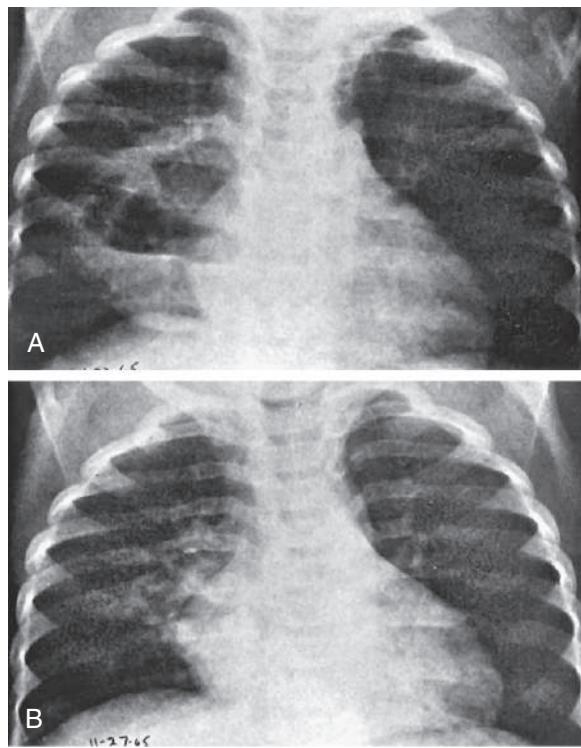


Fig. 453.3 Appearance over a period of 5 days of a large, multiloculated pneumatocele in a segment of alveolar consolidation. A, There is a large cavity with two air-fluid levels in a segment of alveolar pneumonia in the right upper lobe. B, Five days later, the cavity and most of the pneumonic consolidation have disappeared. (From Silverman FN, Kuhn JP. *Essentials of Caffey's Pediatric X-ray Diagnosis*. Chicago: Year Book; 1990:303.)

bacteria are suspected or isolated, piperacillin-tazobactam or a carbapenem should be added. With improvement, oral antibiotics (clindamycin or amoxicillin-clavulanate) can be used to finish the 4 weeks of total therapy. Early CT-guided percutaneous aspiration or drainage has been advocated by some; it may hasten the recovery and shorten the course of parenteral antibiotic therapy. Nonetheless, antibiotic therapy is successful in ~85% of patients with uncomplicated lung abscesses.

For severely ill patients, patients with larger abscess, or those whose status fails to improve after 7-10 days of appropriate antimicrobial therapy, surgical intervention should be considered. Minimally invasive percutaneous aspiration techniques, often with CT guidance, are the initial and, often, only intervention required. Thoracoscopic drainage has also been successfully used with minimal complications. In rare, complicated cases, thoracotomy (e.g., video-assisted thoracoscopic surgery [VATS] with or without bronchoscopic occlusion) with surgical drainage or lobectomy and/or decortication may be necessary. Abscess drainage is reportedly required in ~20% of cases of pulmonary abscess in children.

PROGNOSIS

Overall, the prognosis for children with primary pulmonary abscesses is excellent. The presence of aerobic organisms may be a negative prognostic 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 weeks. Radiologic abnormalities usually resolve in 1-3 months but can persist for years (e.g., B-line artifacts on lung ultrasound). Long-term sequelae can also include air trapping/hyperinflation on lung function testing. With treatment, mortality is typically less than 5%.

Table 453.1 Differential Diagnosis of a Cavitary Lesion on Chest Radiograph

INFECTIOUS CAUSES

Bacteria

Oral anaerobes

Less commonly: *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, enteric gram-negative rods, *Pasteurella multocida*, *Burkholderia cepacia*, *Burkholderia pseudomallei*, *Haemophilus influenzae* types b and c, *Legionella*, group A streptococcus, *Streptococcus pneumoniae*, *Streptococcus anginosus*, *Nocardia*, *Rhodococcus equi*, *Actinomycetes*, *Clostridium*, *Capnocytophaga*

Septic Pulmonary Embolism

Originating in septic phlebitis, including Lemierre syndrome and vegetations from tricuspid endocarditis

Mycobacteria

Tuberculosis and nontuberculous pathogens

Fungi

Endemic mycoses (*Histoplasma*, *Coccidioides*, blastomycosis), *Cryptococcus*, *Aspergillus*, Zygomycetes

Parasites

Paragonimus westermani, *Entamoeba histolytica*, *Echinococcus*

NONINFECTIOUS CAUSES

Neoplasm

Primary lung cancer, metastatic carcinoma (particularly squamous cell)

Pulmonary infarction caused by bland embolus

Vasculitis

Wegener granulomatosis, rheumatoid lung nodule

Airway Disease

Bullae, blebs, or cystic bronchiectasis

Developmental cause

Pulmonary sequestration

Other

Sarcoidosis, achalasia, or transdiaphragmatic bowel herniation giving appearance of cavity with air-fluid level

Modified from Lorber B. Bacterial lung abscess. In: Bennett JE, Dolin R, Blaser M, eds. *Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Elsevier; 2014:855–859.

Table 454.1 Complications of Cystic Fibrosis

RESPIRATORY

Bronchiectasis, bronchitis, bronchiolitis, pneumonia
Atelectasis
Hemoptysis
Pneumothorax
Nasal polyps
Sinusitis
Reactive airway disease
Mucoid impaction of the bronchi
Allergic bronchopulmonary aspergillosis
Cor pulmonale
Respiratory failure

GASTROINTESTINAL

Meconium ileus, meconium plug (neonate)
Meconium peritonitis (neonate)
Distal intestinal obstruction syndrome (non-neonatal obstruction)
Rectal prolapse
Intussusception
Volvulus
Fibrosing colonopathy (strictures)
Appendicitis
Intestinal atresia
Pancreatitis (recurrent)
Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism)
Neonatal obstructive jaundice
Hepatic steatosis
Gastroesophageal reflux
Cholelithiasis
Inguinal hernia
Growth failure (malabsorption)
Vitamin deficiency states (vitamins A, K, E, D)
Insulin deficiency, symptomatic hyperglycemia, diabetes
Malignancy (rare)

OTHER

Infertility (female)
Congenital absence of vas deferens, azoospermia
Delayed puberty
Edema: hypoproteinemia
Dehydration: heat exhaustion
Hyperchloremic metabolic alkalosis: dehydration
Hypertrophic osteoarthropathy: arthritis
Urinary calculi
Clubbing
Amyloidosis
Diabetes mellitus
Aquagenic palmoplantar keratoderma (skin wrinkling)

Adapted from Silverman FN, Kuhn JP. *Essentials of Caffey's Pediatric X-ray Diagnosis*. Chicago: Year Book; 1990:649.

Because CF may manifest as failure to thrive and hepatic dysfunction, including cirrhosis, this disorder enters into the differential diagnosis of many pediatric conditions (Table 454.1).

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 (compared with 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. 454.1).

CF is inherited as an autosomal recessive trait. The *CFTR* gene codes for the *CFTR* protein, which is 1,480 amino acids. *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, but is expressed in other cell types at lower levels. *CFTR* is a member of

Chapter 454

Cystic Fibrosis

Marie E. Egan, Michael S. Schechter, and Judith A. Voynow

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 (*CFTR*) protein, 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.

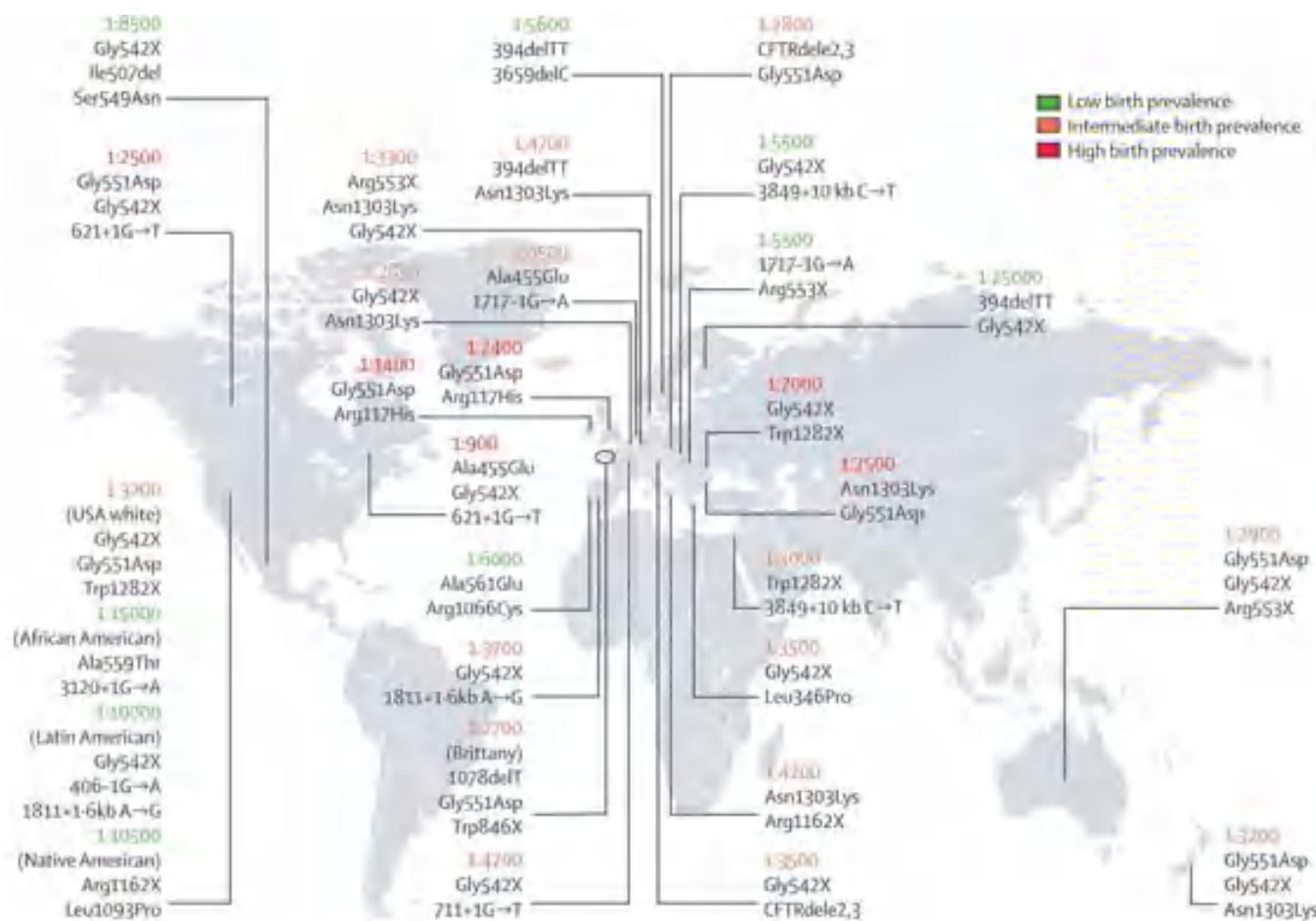


Fig. 454.1 Approximate cystic fibrosis birth prevalence and common pathogenic variants for selected countries. Birth prevalence is reported as the number of live births per case of cystic fibrosis. Common/important pathogenic variants in each region are listed below the prevalence figures. The birth prevalence can vary greatly among ethnic groups in a country. (From O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009;373:1891–1902.)

the adenosine triphosphate (ATP)–binding cassette superfamily of proteins. It functions as an anion channel and is essential for proper chloride and bicarbonate transport across epithelia. More than 1,900 *CFTR* polymorphisms have been described, many of which are not clearly of clinical significance. Those that are associated with clinical manifestations may be grouped into six main classes based on how they affect protein structure and function (Fig. 454.2). Class I–III pathogenic variants are generally considered to be *severe* pathogenic variants in that they lead to a complete or nearly complete absence of *CFTR* function, whereas class IV–VI pathogenic variants are associated with some residual functional protein. The most prevalent pathogenic variant of *CFTR* is the deletion of a single phenylalanine residue at amino acid 508 (*F508del*). This pathogenic variant 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. Nearly 50% of individuals with CF in the United States Cystic Fibrosis Foundation (CFF) Patient Registry are homozygous for *F508del*, and approximately 87% carry at least one *F508del* gene. The remaining patients have an extensive array of pathogenic variants, none of which has a prevalence of more than several percentage points, except in certain populations; for example, the W1282X pathogenic variant occurs in 60% of Ashkenazi Jews with CF. Through the use of probes for 40 of the most common pathogenic variants, the genotype of 80–90% of Americans with CF can be ascertained. Genotyping using a discrete panel of pathogenic variant probes is quick and less costly than more comprehensive sequencing and is the approach typically used in state newborn screening (NBS) programs. In remaining patients, sequencing the entire *CFTR* gene and looking for deletions and duplications are necessary to establish the genotype.

The relationship between *CFTR* genotype and clinical phenotype is highly complex. The *CFTR* pathogenic variant class is strongly associated with pancreatic dysfunction and will usually predict this manifestation in any given patient. Respiratory complications and lung function decline are also correlated with pathogenic variant class severity but with greater variation because of the influence of non-*CFTR* modifier gene polymorphisms and environmental influences on the manifestations of lung disease in any one individual. Studies have identified specific non-*CFTR* modifier genes of importance; genome-wide 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 *ELF5*. A region on chromosome 20 may also be 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. Genome-wide association studies analysis also identified genetic regions that predispose to risk for liver disease, CF-related diabetes, and meconium ileus.

The high frequency of *CFTR* pathogenic variants has been ascribed to resistance to the morbidity and mortality associated with infectious dysenteries through the ages. Cultured CF intestinal epithelial cells homozygous for the *F508del* pathogenic variant 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.

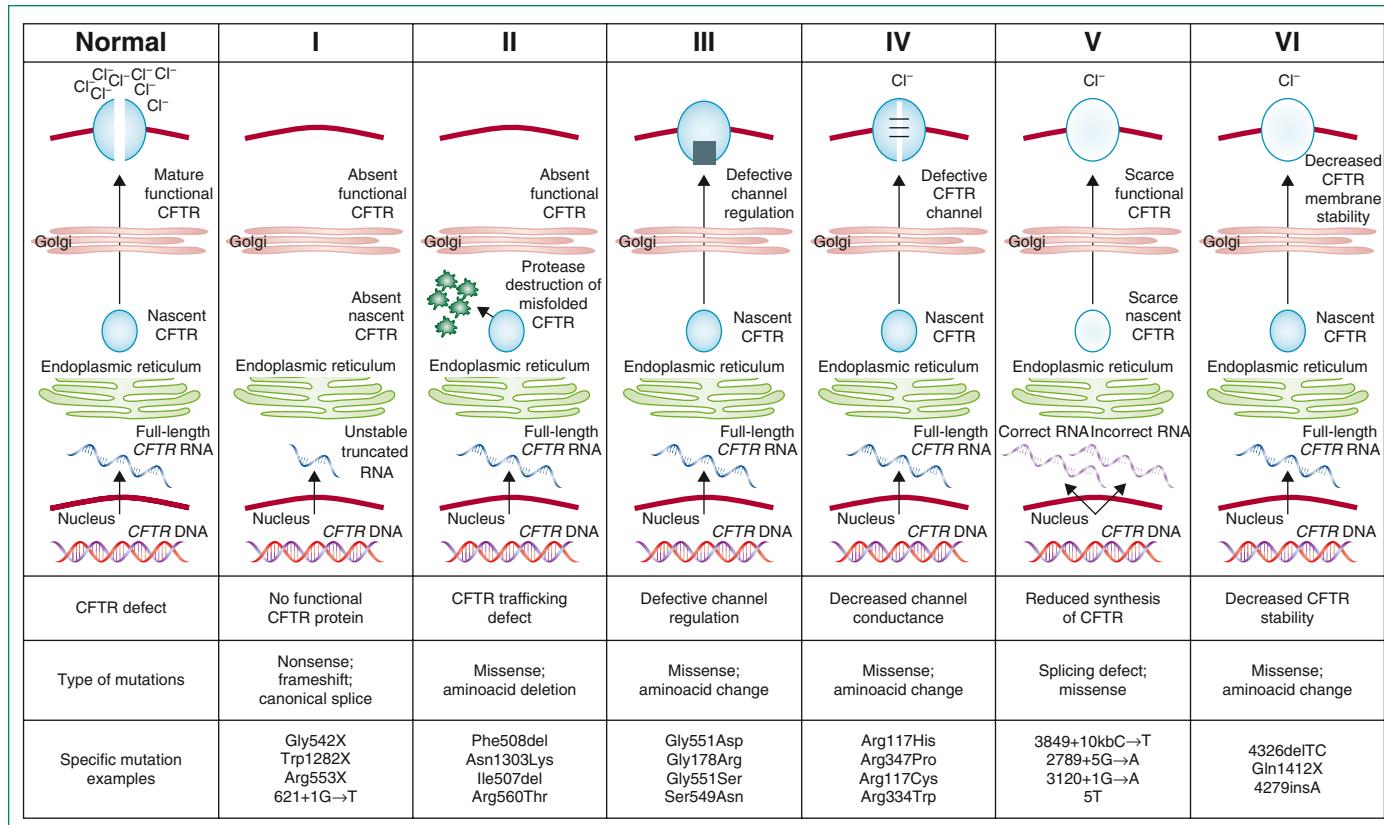


Fig. 454.2 Classes of cystic fibrosis transmembrane conductance regulator (CFTR) pathogenic variants. Pathogenic variants in the CFTR gene can be divided into six classes. Class I pathogenic variants result in no protein production. Class II pathogenic variants (including the most prevalent, Phe508del) cause retention of a misfolded protein at the endoplasmic reticulum and subsequent degradation in the proteasome. Class III pathogenic variants affect channel regulation, impairing channel opening (e.g., Gly551Asp). Class IV pathogenic variants show reduced conduction—that is, decreased flow of ions (e.g., Arg117His). Class V pathogenic variants cause substantial reduction in mRNA or protein, or both. Class VI pathogenic variants cause substantial plasma membrane instability and include Phe508del when rescued by most correctors (rPhe508del). (From Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. *Lancet Respir Med*. 2013;1:158–163.)

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. In addition, 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 or bicarbonate in response to cyclic adenosine monophosphate-mediated signals, and at least in the respiratory epithelial cells, excessive amounts of sodium are absorbed through these membranes. These defects can be traced to a dysfunction of CFTR. CFTR function is highly regulated and energy dependent; it requires both cyclic adenosine monophosphate-stimulated protein kinase A phosphorylation of the regulatory domain and ATP binding and hydrolysis at the nucleotide binding domains. CFTR also interacts with other ion channels, signal transduction proteins, and the cytoskeleton (Fig. 454.3 and see Fig. 454.2).

Many hypotheses have been postulated to explain how CFTR dysfunction results in the clinical phenotype (Fig. 454.4). It is likely that no one hypothesis explains the full spectrum of disease. One model is that airway hydration homeostasis requires both CFTR and P2Y₂-regulated calcium-activated chloride secretion. When extracellular ATP is depleted, such as after viral infections, calcium-activated chloride secretion is not activated, and the failure of CFTR chloride secretion results in dehydrated airway secretions, increased concentration of mucin solids, and more viscoelastic mucus that is not cleared by normal mucociliary transport. Another mechanism that

is supported by both primary human airway studies and investigations in the CF pig is that variant CFTR causes failure of HCO₃⁻ secretion and a more acidic airway surface liquid, which increases mucous viscoelasticity, resulting in poor mucociliary clearance. Mucous secretions are tethered to submucosal gland ducts and 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. CFTR dysfunction in airway smooth muscle has been implicated in tracheal and airway abnormalities in humans and in animal models of the disease (pig and mice). These data suggest that CFTR expression in this nonepithelial tissue contributes to airway constriction.

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. One explanation for infection is a sequence of events starting with failure to clear inhaled bacteria promptly and then proceeding to persistent infection and an inflammatory response in airway walls. Another explanation for early infection is the failure of innate immune proteins to kill bacteria in an abnormally acidic airway milieu. In addition, it has 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 (including macrophage, neutrophils, lymphocytes, and

Fig. 454.3 Schematic diagram depicting cystic fibrosis (CF) epithelial channel defects, characterized by impaired chloride secretion, massive sodium absorption, and movement of water through the epithelium, leading to a dehydrated airway surface. ADP, Adenosine diphosphate; ATP, adenosine triphosphate; CFTR, cystic fibrosis transmembrane conductance regulator; ClCa, alternative chloride channel; ENaC, epithelium sodium channel; PKA, protein kinase A. (From Michelson P, Faro A, Ferkol T. Pulmonary disease in cystic fibrosis. In Wilmott RW, Deterding RR, Li A et al., eds. Kendig's Disorders of the Respiratory Tract in Children, 9th ed. Philadelphia: Elsevier; 2019: Fig. 51.1, p. 778.)

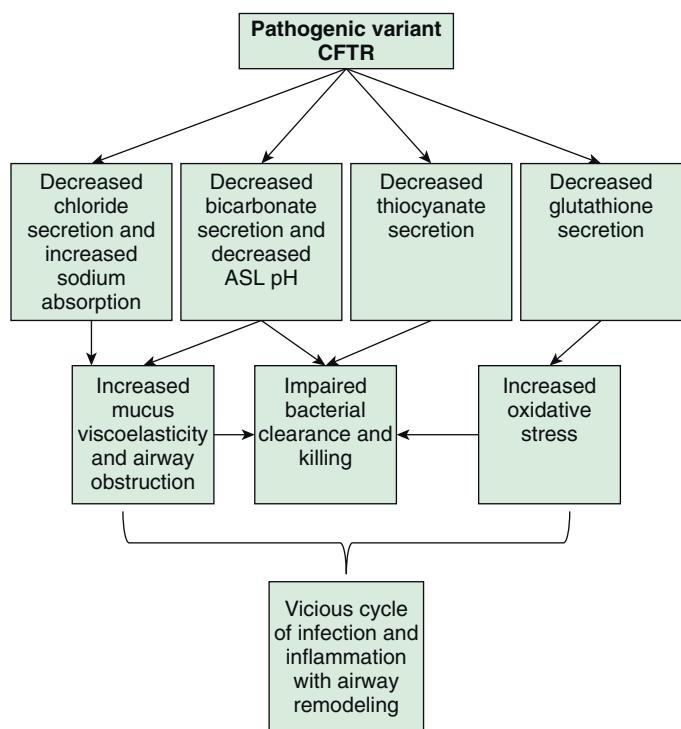
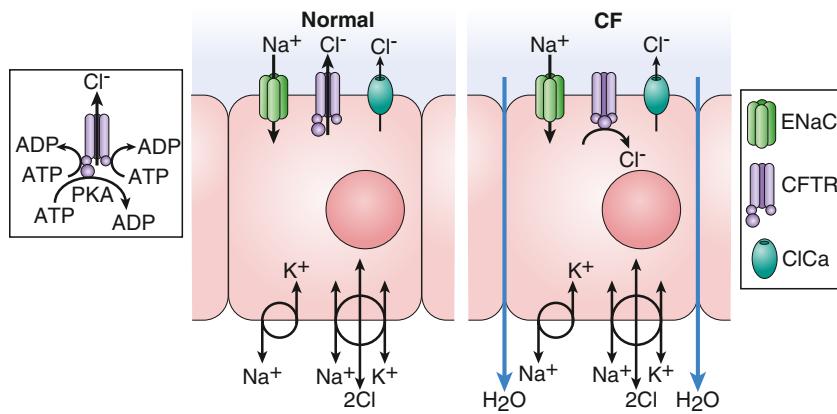


Fig. 454.4 Schema of variant cystic fibrosis transmembrane conductance regulator (CFTR) mechanisms of chronic airway disease. CFTR conducts several anions, including chloride, bicarbonate, thiocyanate, and glutathione. The loss of CFTR function affects critical airway epithelial functions: (1) It increases the risk for dehydration of airway surface liquid (ASL) with loss of chloride efflux and associated increased sodium channel activity. (2) The loss of secreted bicarbonate and/or acidic pH of the ASL increases mucous viscoelasticity resulting in failure of mucociliary transport. (3) Acidic pH in the ASL impairs normal innate immune clearance of bacteria. (4) Loss of thiocyanate impairs lactoperoxidase bacterial killing. (5) Loss of glutathione secretion depletes the antioxidant capacity of the airway resulting in increased inflammation, increased mucus secretion, and increased mucous viscoelasticity. These factors lead to a vicious cycle of infection and inflammation that is progressive.

dendritic cells) and have suggested that these alterations contribute to this proinflammatory state and to a dysregulated immune response. It appears that inflammatory events occur first in small airways, perhaps because it is more difficult to clear altered secretions and microorganisms from these regions. The agents of airway injury include neutrophil products, such as oxidative radicals and proteases, and immune reaction products. These inflammatory products further aggravate airway obstruction by increasing mucus secretion and altering mucus structure to promote both intramolecular and intermolecular interactions.

Excessive inflammatory cell polymers in CF sputum, including DNA, filamentous actin, and glycosaminoglycans, further contribute to abnormal mucous viscoelastic properties and airway obstruction. Chronic bronchiolitis and bronchitis are the initial lung manifestations (see Chapter 439), but after months to years, structural changes in airway walls produce bronchiolectasis and **bronchiectasis**. With advanced lung disease, infection may extend to peribronchial lung parenchyma.

A central feature of lung disease in patients with CF is the high prevalence of airway infection with *Staphylococcus aureus* (see Chapter 227.1), *Pseudomonas aeruginosa* (see Chapter 251.1), and *Burkholderia cepacia* complex (see Chapter 251.2), 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.

Altered lipid homeostasis has been implicated as a predisposing factor for respiratory tract infection and inflammation. Concentrations of lipoxins—molecules that suppress neutrophilic inflammation—are suppressed in CF airways. There is an imbalance of lipids with increased arachidonic acid and decreased docosahexaenoic acid, which promotes inflammation. There is also an imbalance of ceramide in the CF airway that is proinflammatory. Supporting the idea that altered lipid uptake affects infection and inflammation is the observation that the 10–15% of individuals with CF who retain substantial exocrine pancreatic function have delayed acquisition of *P. aeruginosa* and slower deterioration of lung function. However, it appears that nutritional factors are contributory only because preservation of pancreatic function does not preclude development of typical lung disease.

The variation in progression of lung disease seen in patients with CF is also influenced by social and physical environment factors, whose impact matches that of the CFTR genotype. Exposure to environmental tobacco smoke and outdoor air pollutants and early acquisition of respiratory virus infections, as well as pathogenic organisms like *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA), have been implicated as causes of worsening disease. Sex/gender disparities also seem to exist, with females having a poorer prognosis. Although studies have suggested that estrogen may influence disease exacerbations, the gap seems to be narrowing.

Although most CF care is delivered at specialty centers and is broadly influenced by current clinical guidelines, there is enough variability in treatment approaches to cause large variation in respiratory and

nutritional outcomes across the care networks in both North America and Europe. Social determinants of health are associated with significant disparities in outcome; socioeconomic status has been shown to be a strong predictor of mortality, as well as both nutritional status and lung function on both sides of the Atlantic. The specific mechanism of effect is unclear, but evidence suggests a role for socioeconomic status-related differences in health behaviors and disease self-management practices, stress and mental health issues, and environmental tobacco smoke exposure. Differential access to specialty care and medications are also known to affect clinical outcomes.

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, mucous accumulation and inflammation extend to the larger airways (*bronchitis*) (see Chapter 439.2). Goblet cell hyperplasia and submucosal gland hypertrophy become prominent pathologic findings, which is most likely a response to chronic airway infection. Organisms appear to be confined to the endobronchial space; invasive bacterial infection is not characteristic. With long-standing disease, evidence of airway destruction such as **bronchiolar obliteration**, **bronchiolectasis**, and **bronchiectasis** (see Chapter 452) 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, with 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 429). 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 second 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 adequate nutrition. At autopsy, hepatic congestion secondary to cor pulmonale can be 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

Since the universal adoption of CF NBS, along with the evolution of aggressive and proactive treatment approaches, the clinical face of CF is quite different from what it was in earlier decades. Diagnosis is typically accomplished before 1 month of age, before any obvious clinical symptoms or signs, and treatment is targeted at immediately correcting nutritional deficiencies and delaying the respiratory complications of the disease. The interaction of pathogenic variant heterogeneity and environmental factors leads to highly variable involvement of the lungs, pancreas, and other organs. A summary of the time course of potential development of clinical manifestations is shown in Figure 454.5.

Respiratory Tract

Infants diagnosed by CF NBS are generally asymptomatic from a respiratory standpoint. Nonetheless, the majority are infected with *S. aureus*, *Haemophilus influenzae*, or even *P. aeruginosa* within the first month of life, and chest CT scans show characteristic heterogeneous air trapping in ~65% of infants by their first birthday, and bronchiectasis is found in more than

Sinopulmonary		
Infancy	Gastrointestinal	
• Infection	• ABPA • Sinusitis • Polyposis	• ABPA • Haemoptysis, pneumothorax • Respiratory failure • Sinusitis, polyposis, anosmia
Gastrointestinal		
• Fetal echogenic bowel • Meconium ileus • Pancreatic insufficiency • Rectal prolapse	• DIOS • Intussusception • Hepatic steatosis, biliary fibrosis • Rectal prolapse	• DIOS • Intussusception • Biliary fibrosis, cirrhosis • Digestive tract cancer (adenocarcinoma)
Renal, endocrine, other		
• Dehydration • Hyponatraemic hypochloraemic metabolic alkalosis	• Renal calculi • Hyponatraemic hypochloraemic metabolic alkalosis	• Delayed puberty, osteoporosis, CFRD • Renal calculi, renal failure • CBAVD, HPOA • Arthritis, vasculitis • Hyponatraemic hypochloraemic metabolic alkalosis

Fig. 454.5 Approximate age of onset of clinical manifestations of cystic fibrosis. ABPA, Allergic bronchopulmonary aspergillosis; CBAVD, congenital bilateral absence of the vas deferens; CFRD, cystic fibrosis-related diabetes mellitus; DIOS, distal intestinal obstruction syndrome; HPOA, hypertrophic pulmonary osteoarthritis. (From O'Sullivan BP, Freedman SD. *Cystic fibrosis*. Lancet. 2009;373:1891–1902.)

10% of 1-year-olds and ~60% of 5-year-olds. The earliest symptom is usually a cough that may begin with a viral respiratory tract infection but then persists unless treated with antibiotics. With treatment, the generally realized goal is for patients to remain asymptomatic throughout childhood, except for the periodic development of cough, chest congestion, sputum production, and/or wheezing that define a *pulmonary exacerbation*.

The rate of progression of lung disease is the chief determinant of morbidity and mortality. As lung disease slowly progresses, chronic cough, sputum production, exercise intolerance, shortness of breath, and inability to maintain weight are noted. Common pulmonary complications include atelectasis, hemoptysis, and pneumothorax; these usually appear in late adolescence or beyond. Cor pulmonale, respiratory failure, and death eventually supervene unless lung transplantation is accomplished; this has become increasingly uncommon in childhood. Infection with certain strains of *B. cepacia* and other multidrug-resistant organisms such as non-tuberculous mycobacteria may be associated with particularly rapid pulmonary deterioration.

Children with CF are unlikely to exhibit any abnormal findings on physical exam except during pulmonary exacerbations. Eventual physical findings include increased anteroposterior diameter of the chest, generalized hyperresonance, scattered or localized coarse crackles, and digital clubbing. Expiratory wheezes may be heard, a manifestation of airway inflammation and edema that may or may not be associated with bronchodilator responsiveness. Cyanosis is a late sign. Even though the paranasal sinuses are virtually always opacified radiographically, acute sinusitis is infrequent. Nasal obstruction, rhinorrhea, and anosmia are common, caused by inflamed, swollen mucous membranes or, in some cases, nasal polypsis. Nasal polyps are most troublesome between 5 and 20 years of age and often require repeated surgeries to control.

Intestinal Tract

In 15–20% of newborn infants with CF, the ileum is completely obstructed by meconium (**meconium ileus**). The frequency is greater among siblings born subsequent to a child with meconium ileus, and concordance is particularly striking in monozygotic twins, reflecting a genetic contribution from one or more unknown modifying genes. Abdominal distention, emesis, and failure to pass meconium appear in the first 24–48 hours of life (see Chapter 135) and often require surgical intervention. Abdominal radiographs (Fig. 454.6) 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. These infants may need bowel resection, leading to significant nutritional challenges caused by short bowel syndrome superimposed upon pancreatic insufficiency.

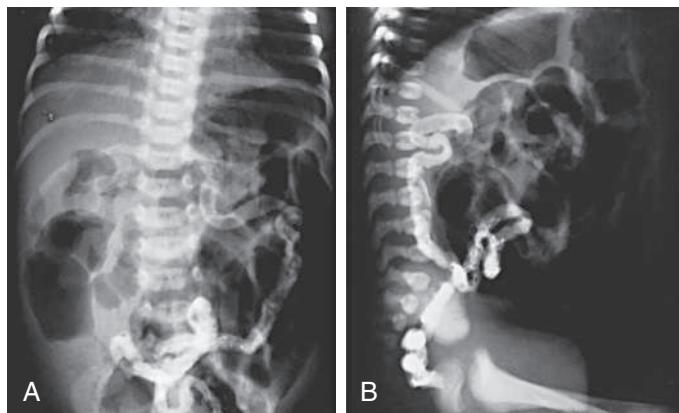


Fig. 454.6 A and B, Contrast enema study in a newborn infant with abdominal distention and failure to pass meconium. Notice the small diameter of the sigmoid and ascending colon and dilated, air-filled loops of small intestine. Several air-fluid levels in the small bowel are visible on the upright lateral view.

Constipation and ileal obstruction with fecal material (**distal intestinal obstruction syndrome [DIOS]**) occur in older children, causing cramping abdominal pain, abdominal distention, and obstruction that can be treated with medical approaches to bowel evacuation—typically oral hyperosmotic polyethylene glycol preparations, and occasionally, in more severe cases, hyperosmotic contrast enemas.

More than 85% of children with CF have *exocrine pancreatic insufficiency*, causing protein and fat malabsorption. Symptoms, if untreated, include frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large. Weight gain can be challenging, but attainment of normal growth and development is an expectation of treatment. A protuberant abdomen, decreased muscle mass, poor growth, and delayed maturation are classic and rarely seen physical signs. Excessive flatus may be a problem even in well-nourished children. Supplementation with fat-soluble vitamin preparations has made deficiencies of vitamins A, E, and K unusual, but vitamin D deficiency continues to be prevalent, and although rickets is rare, osteoporosis is common, especially in older patients and those with more severe lung disease. Class IV–VI pathogenic variants are associated with *pancreatic sufficiency*, but patients with these pathogenic variants are prone to recurrent pancreatitis when they reach adolescence.

Historically a relatively common event, **rectal prolapse** occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy.

Biliary Tract

Infants may occasionally present with **neonatal jaundice** suggestive of biliary obstruction. Evidence of later liver dysfunction is most often detected in the first 15 years of life and can be found in up to 30% of individuals. **Biliary cirrhosis** develops in about 5–7% of patients. Manifestations can include icterus, ascites, hematemesis from esophageal varices, and evidence of hypersplenism. Biliary colic secondary to cholelithiasis may occur in the second decade or later. Liver disease occurs independent of genotype but is associated with meconium ileus and pancreatic insufficiency.

Cystic Fibrosis–Related Diabetes and Pancreatitis

Endocrine pancreatic insufficiency tends to develop in the second decade and beyond and is more common in patients with a family history of type 2 diabetes mellitus. It most commonly begins with postprandial hyperglycemia and may or may not be accompanied by weight loss or flattening weight gain. Fasting hyperglycemia and elevated hemoglobin A_{1c} are later manifestations. Ketoacidosis usually does not occur because insulin deficiency is relative and not absolute, but eye, kidney, and other vascular complications have been noted in patients living ≥ 10 years after the onset of hyperglycemia. Recurrent acute pancreatitis occurs occasionally in adolescents and adults who have residual function CFTR pathogenic variants with exocrine pancreatic sufficiency.

Genitourinary Tract

Virtually all males are **azoospermic** because of failure of development of wolffian duct structures, but sexual function is generally unimpaired. The female fertility rate is diminished, especially in women who have poor nutrition or advanced lung disease. Pregnancy is generally tolerated well by women with good pulmonary function but may accelerate pulmonary progression in those with advanced lung disease and may lead to glucose intolerance that persists after the pregnancy is over. 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 may 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 relatively normal sweat chloride values.

DIAGNOSIS AND ASSESSMENT

CF is diagnosed when an individual has both a clinical presentation of the disease (such as elevated immunoreactive trypsinogen in the newborn period or signs and symptoms discussed earlier in older patients) and evidence of CFTR dysfunction (physiologic assays and/or the presence of disease-causing CFTR genetic variants) (Table 454.2). This simple formulation is complicated by the existence of CFTR genetic variants that are associated with little or no compromise of CFTR function and are therefore of no or varying clinical consequence, leading to a number of patients who fall into “gray” areas.

DIAGNOSIS OF CF VIA NEWBORN SCREENING

All CF NBS algorithms begin in the first days of life with the measurement of serum immunoreactive trypsinogen (IRT), a pancreatic proenzyme that is elevated in almost all infants with CF. Because IRT levels can fluctuate day by day and season by season, most states set a cutoff level based on an average of IRT levels (e.g., $\geq 95\%$ percentile). Depending on the state, three different CF NBS algorithms are used:

1. IRT/DNA: This is the most commonly used algorithm. A CFTR gene pathogenic variant screening panel (whose composition varies by state) is applied to the original blood spot. Because not all pathogenic variants are included in the screening panel, the finding of just one CFTR pathogenic variant represents a positive screen. Some states (California, New York) perform gene sequencing from the dried blood spot in response to finding one CFTR gene pathogenic variant.
2. IRT/IRT: The IRT is repeated 2–4 weeks later. In infants without CF, the second IRT is usually normal, whereas in infants with CF, it is persistently elevated, representing a positive screen. This approach has been shown to have lower sensitivity than IRT/DNA.
3. IRT/IRT/DNA: Lower cutoffs are used for IRT than in the states with IRT/IRT algorithms, and in infants with persistently elevated IRT, pathogenic variant screening is performed, and the finding of at least one pathogenic variant represents a positive screen.

A positive CF NBS test only identifies infants with a high likelihood of having CF, but it is not diagnostic for CF. Any infant with a positive CF NBS test should have a sweat chloride test (SCT) performed to confirm the diagnosis of CF. In states using the IRT-IRT algorithm, about 20% of those who have a positive CF NBS are subsequently diagnosed with CF by SCT. In states using the IRT-DNA algorithm, only about 10% of infants who are found to have just one CF-causing pathogenic variant from the screening panel are found to have CF (depending on the pathogenic variant screening panel and ethnic background of the child). Even in cases where two CF-causing pathogenic variants have

Table 454.2 Diagnostic Criteria for Cystic Fibrosis (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)
or
A history of CF in a sibling
or
A positive newborn screening test
plus
Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:
Two elevated sweat chloride concentrations obtained on separate days
or
Identification of two CF pathogenic variants
or
An abnormal nasal potential difference measurement

been identified, sweat testing is indicated to rule out laboratory error or misidentification of newborn blood spots.

DIAGNOSIS OF CYSTIC FIBROSIS OUTSIDE OF NEWBORN SCREENING

Although most cases of CF are diagnosed through NBS, there is still a need to consider the diagnosis in the occasional older patient. This is because NBS is not performed everywhere, and even for individuals who were screened, there is the possibility of a false negative. Most older patients whose diagnosis was missed early in life will have unusual class IV, V, or VI pathogenic variants and therefore *normal* pancreatic function. A CF diagnosis in individuals outside of NBS relies on (1) clinical evidence, such as a chronic productive cough resulting from either bronchitis or chronic sinusitis, nasal polyps, allergic broncho-pulmonary aspergillosis or unexplained bronchiectasis, congenital bilateral absence of the vas deferens (CBAVD) (in males) or recurrent pancreatitis, and (2) evidence of CFTR dysfunction (such as CFTR molecular genetic analysis, SCT, or other CFTR physiologic tests).

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 the diagnosis of CF. The procedure requires meticulous attention to detail, and its accuracy can only be assumed when performed at CF Foundation-accredited care centers. An electric current is used to carry pilocarpine into the skin of the forearm and locally stimulate the sweat glands because the measurement is validated under conditions of maximal sweat production. Sweat testing is accurate at any postnatal age, but adequate sweat rates are harder to attain in infants less than 36 weeks gestational age and/or less than 2 kg in weight. Positive results should be confirmed; for a negative result, the test should be repeated if suspicion of the diagnosis remains.

More than 60 mmol/L of chloride in sweat is diagnostic of CF when one or more criteria are present. In individuals with a positive NBS, a sweat chloride level less than 30 mmol/L indicates that CF is unlikely. Borderline (or intermediate) values of 30–59 mmol/L have been reported in patients of all ages who have CF with atypical involvement and require further testing. Table 454.3 lists the conditions associated with false-negative and false-positive sweat test results.

Table 454.3 Conditions Associated with False-Positive and False-Negative Sweat Test Results

WITH FALSE-POSITIVE RESULTS
Eczema (atopic dermatitis)
Ectodermal dysplasia
Malnutrition/failure to thrive/deprivation
Anorexia nervosa
Congenital adrenal hyperplasia
Adrenal insufficiency
Glucose-6-phosphatase deficiency
Mauriac syndrome
Fucosidosis
Familial hypoparathyroidism
Hypothyroidism
Nephrogenic diabetes insipidus
Pseudohypoaldosteronism
Klinefelter syndrome
Familial cholestasis syndrome
Autonomic dysfunction
Prostaglandin E infusions
Munchausen syndrome by proxy

WITH FALSE-NEGATIVE RESULTS
Dilution
Malnutrition
Edema
Insufficient sweat quantity
Hyponatremia
Cystic fibrosis transmembrane conductance regulator pathogenic variants with preserved sweat duct function

DNA Testing

Several commercial laboratories provide screening panels that test for the most common CFTR pathogenic variants. The American College of Medical Genetics recommends at least 23; other panels screen for >100 pathogenic variants. The sensitivity of these panels depends on the race/ethnicity of the population tested, but is always well under 100%, so it is important to view them as screening, but not definitive, diagnostic tests. Whole CFTR gene sequencing with additional attention to deletions and duplications is available but is expensive and only helpful in very select situations.

Other Physiologic Measures of CFTR Function

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. Intestinal current measurements may also provide additional helpful information, particularly in children who are unable to cooperate with nasal potential difference testing. These procedures are primarily used in research applications and have never undergone extensive validation as a clinical tool.

OTHER LABORATORY TESTING OF IMPORTANCE IN DIAGNOSIS AND MANAGEMENT

Pancreatic Function

The diagnosis of pancreatic insufficiency 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. The quantification of fat malabsorption with a 72-hour stool collection is rarely performed in the clinical setting. CF-related diabetes affects approximately 20% of adolescents and 40–50% of adults, and clinical guidelines recommend yearly oral glucose tolerance testing (OGTT) after age 10. OGTT may sometimes be clinically indicated at an earlier age. Spot testing of blood and urine glucose levels and glycosylated hemoglobin levels are not sufficiently sensitive.

Radiology

Hyperinflation of lungs occurs early and is often accompanied by non-specific peribronchial thickening (Fig. 454.7). 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.

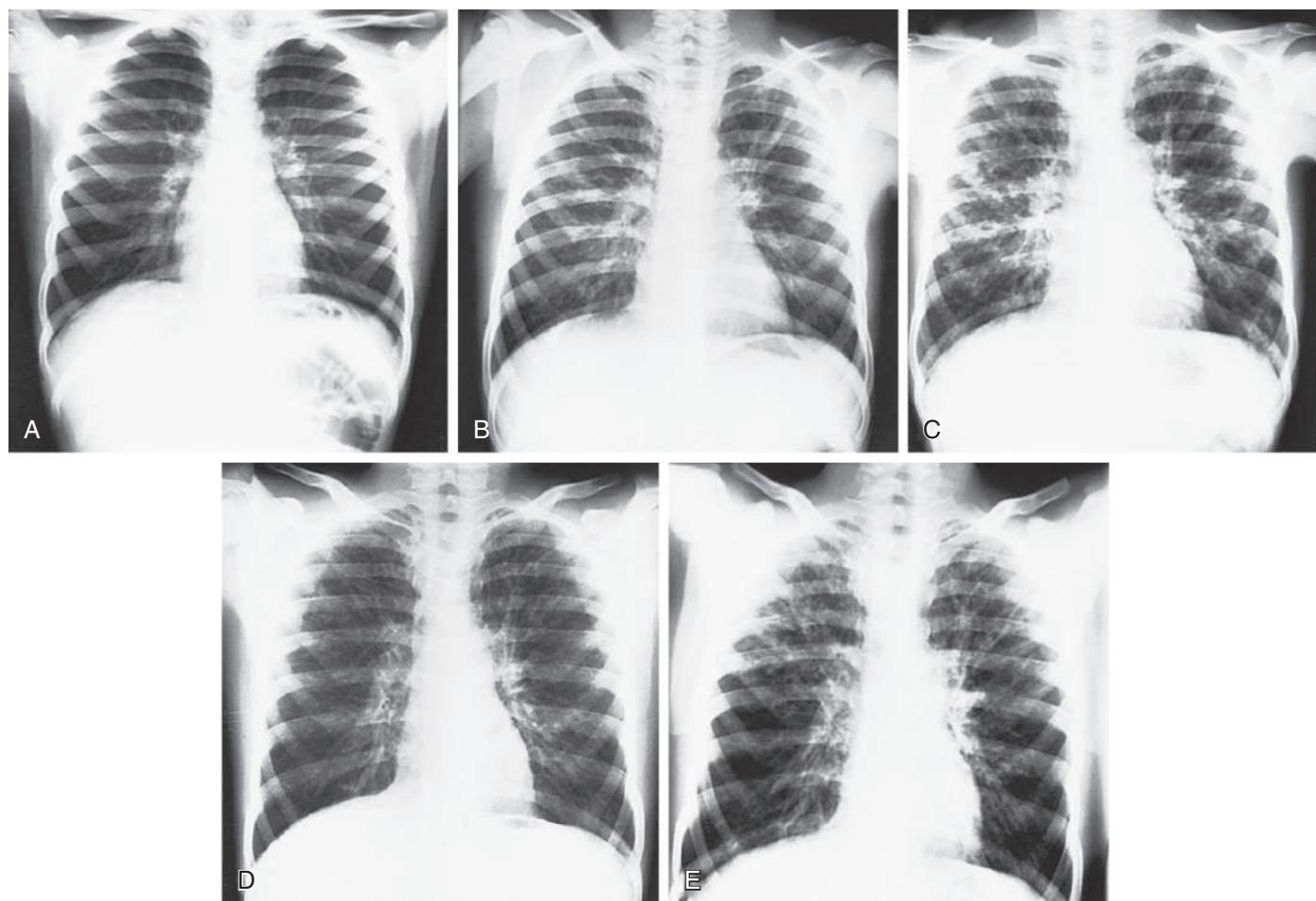


Fig. 454.7 Serial radiographs in a child show the changing appearance of cystic fibrosis over 6 yr. A, At 9 yr, frontal radiograph shows minimal peribronchial thickening and hyperaerated lungs indistinguishable from asthma. B, Nineteen mo later, the radiographic picture has worsened considerably. Extensive 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 mo later, further deterioration is obvious. Widespread typical changes of cystic fibrosis (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 yr 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 T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008: Fig. 73-54.)

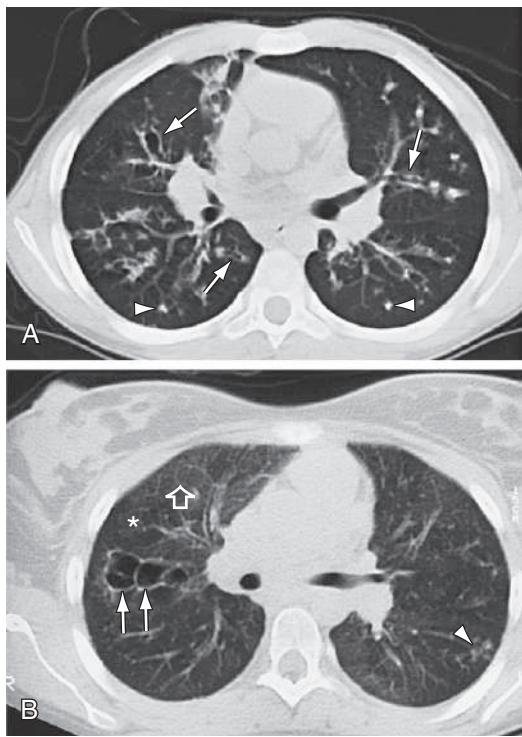


Fig. 454.8 CT scans of the chest in cystic fibrosis. A, A 12-yr-old male with moderate lung disease. Airway and parenchymal changes are present throughout both lungs. Multiple areas of bronchiectasis (arrows) and mucous plugging (arrowheads) can be seen. B, A 19-yr-old female has mostly normal lung with one area of saccular bronchiectasis in the right upper lobe (arrows) and a focal area of peripheral mucous plugging in the left lower lobe (arrowhead). Lung density is heterogeneous with areas of normal lung (open arrow) and areas of low attenuation reflecting segmental and subsegmental air trapping (asterisk).

Cyst formation, extensive bronchiectasis, dilated pulmonary artery segments, and segmental or lobar atelectasis is often apparent with advanced disease. Most CF centers obtain chest radiographs (posteroanterior [PA] and lateral) at least annually. CT of the chest can detect heterogeneous hyperinflation and localized thickening of bronchial airway walls, mucous plugging, focal hyperinflation, and bronchiectasis (Fig. 454.8). CT abnormalities are commonly seen as early as the first year of life and even in asymptomatic children with normal lung function.

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 show pancreatic changes indicative of CF and suggest ileal obstruction with meconium early in the second trimester, but this finding is not predictive of meconium ileus at birth.

Pulmonary Function

Infant pulmonary function testing is done routinely for clinical evaluation at a few CF centers, but given its complexity and the need for sedation, for the most part it is reserved for research protocols. Lung clearance index (LCI), measured by multiple breath washout, can be done in infants and young children and is a sensitive measure of ventilation inhomogeneity caused by small airways disease. Currently it is primarily used for research, but given its ease and applicability, it may be adopted as a standard monitoring tool in the future as CF care centers become more accustomed to its use.

Standard pulmonary function studies are usually obtained starting at about 4 years of age and are routinely done by age 6. **Forced expiratory volume in 1 second** (FEV₁) is the measurement that has been shown to correlate most closely with mortality and shows a gradual decline averaging 2–3% per year throughout childhood. Although a small number of children may already show evidence of airway obstruction

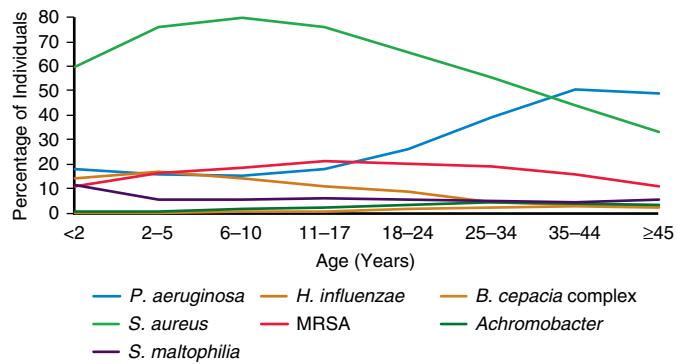


Fig. 454.9 Prevalence of respiratory microorganisms by age cohort, 2021. (From the Cystic Fibrosis Patient Registry 2021. Annual Data Report. p. 30. © 2022 Cystic Fibrosis Foundation. Bethesda, Maryland. <https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf>)

by age 6, trends over the past several decades, as reported by the CFF patient registry, show a steady improvement in average FEV₁ of the CF population. The proportion of people with CF age 18 years who are in the normal/mild lung disease category (FEV₁ $\geq 70\%$ predicted) has increased from 33.8% in 1989 to 78.3% in 2019. The proportion in the severe lung disease category (FEV₁ $< 40\%$ predicted) has decreased from 24.0% in 1988 to 2.6% in 2019. Residual volume and functional residual capacity are increased early in the course of lung disease and are the cause of decreasing forced vital capacity (FVC) measurement. 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 clinically significant decrements are documented—an acute drop in FEV₁ is probably the most sensitive indicator of a pulmonary exacerbation that should be treated with systemic antibiotics.

Microbiologic Studies

H. influenzae and *S. aureus* are the most common organisms recovered in young children (Fig. 454.9). *Pseudomonas* may be acquired early and is an organism of key significance. *P. aeruginosa* appears to have a special propensity for the CF airway and over time characteristically develops a biofilm associated with a mucoid appearance in the microbiology lab and which correlates with more rapid progression of lung disease. Once *P. aeruginosa* develops a mucoid phenotype, it is extremely difficult to eradicate from the airway. A wide range of other organisms are frequently recovered, particularly in advanced lung disease; they include a variety of gram-negative rods, including the *B. cepacia* complex, which may be associated with a fulminant downhill course (**cepacia syndrome**); *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*; assorted fungi, especially *Aspergillus fumigatus*, which is most important because of the relatively common development of **allergic bronchopulmonary aspergillosis**; and nontuberculous mycobacterial species, especially *Mycobacterium avium* complex and *Mycobacterium abscessus*. Airway cultures are obtained regularly, most typically using oropharyngeal swabs in young children, and then sputum (which may be induced) in older children capable of expectoration. Oropharyngeal swabs typically give a good indication of the lower airway flora, but fiberoptic bronchoscopy may be used to gather lower respiratory tract secretions of infants and young children who do not expectorate if there is a concern for false-negative cultures, especially regarding the presence of *P. aeruginosa*.

The CF airway microbiome consists of a large number of additional organisms, especially anaerobes that are identified through antigen detection but not culture methods. The significance of this finding and its therapeutic implications remain somewhat unclear, but it has long been appreciated that response to antibiotic treatment of pulmonary exacerbations is not always predictable based on culture and sensitivity of airway cultures.

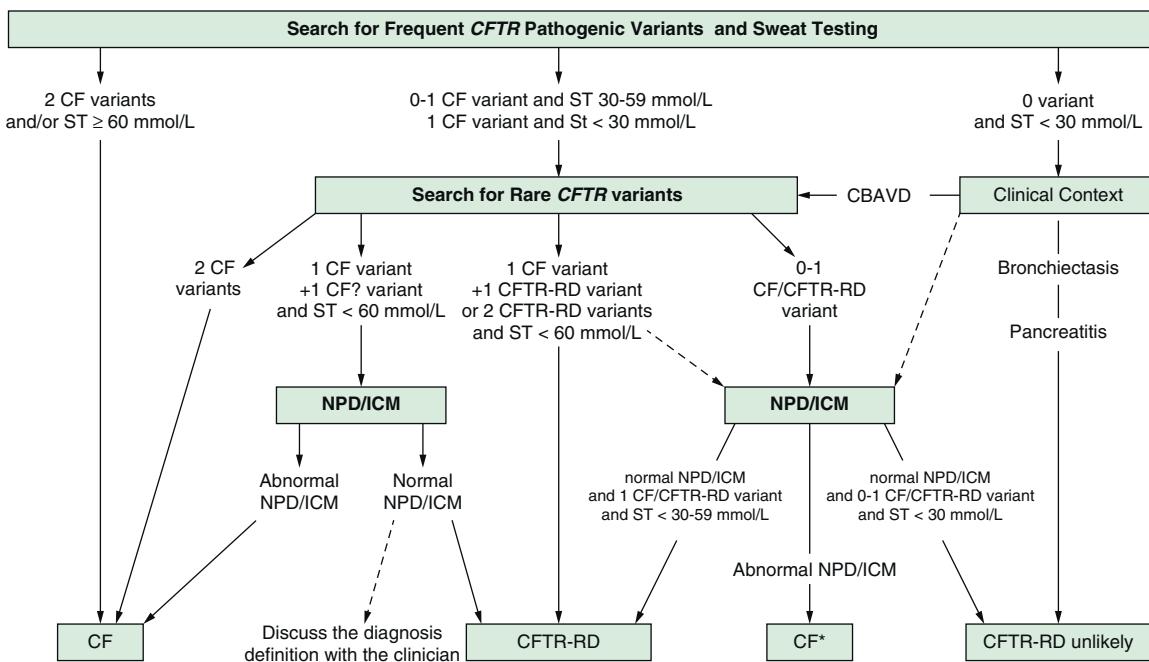


Fig. 454.10 2015 European Cystic Fibrosis Society recommended algorithm for diagnosis of CFTR-RD. Global diagnostic algorithm for CF and CFTR-RD. A global flowchart of genetic and functional diagnostic testing in CF and CFTR-RD is presented. CBAVD, Congenital bilateral absence of the vas deferens; CF, cystic fibrosis; CF? pathogenic variant of unproven or uncertain clinical significance; CF*, diagnosis of CF or consider this diagnosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTR-RD, CFTR-related disorders; ICM, intestinal current measurement; NPD, nasal potential difference; ST, sweat test (repeated; false positive should be excluded/sought in a specialized center). (From Bombieri C, Clastres M, De Boeck K, et al. Recommendations for the classification of diseases as CFTR-related disorders. *J Cyst Fibros*. 2011;10[Suppl 2]:S86–102, Fig 1.)

MANIFESTATIONS OF REDUCED CFTR FUNCTION THAT DO NOT MEET CRITERIA FOR CF

CFTR-Related Metabolic Syndrome

There is a subset of infants with a positive newborn screen for CF who have inconclusive diagnostic testing. The term for this condition, used in the United States, is *CFTR-related metabolic syndrome* (CRMS); in Europe, the analogous term is *CF screen positive, inconclusive diagnosis* (CFS-PID). Data from the CF Foundation National Patient Registry show that approximately one infant is diagnosed with CRMS for every five cases of CF. An infant is determined to have CRMS if they are asymptomatic with a positive CF NBS test and either (1) sweat test <30 mmol/L and two *CFTR* pathogenic variants, at least one of which has unclear phenotypic consequences, or (2) sweat test 30–59 mmol/L and zero or one CF-causing CFTR pathogenic variant.

CRMS should be distinguished from CFTR-related disorder (CFTR-RD), described later, in that CRMS is a diagnosis that arises only from CF NBS in otherwise asymptomatic individuals.

Data on long-term outcomes of infants with CRMS are limited because universal CF NBS is relatively new and CRMS has only recently been recognized. The majority of CRMS infants appear to have normal growth and do not develop any pulmonary manifestations of CF, although it is not unusual for them to grow *P. aeruginosa* from their airways in the absence of any other clinical manifestations. However, a small percentage (~5–10%) will develop signs and symptoms of CF, including measures of CFTR dysfunction such as a clinically elevated sweat chloride or abnormalities in other CFTR functional assays. This is a diagnosis that it is important for the general pediatrician to be aware of, because these children are often lost to follow-up by CF care centers.

CFTR-Related Disorder

The diagnosis of CFTR-RD has been defined as a monosymptomatic clinical entity associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF. Common manifestations include CBAVD, recurrent pancreatitis, chronic sinusitis, nasal polypsis, or bronchiectasis. This is more typically diagnosed in adults but sometimes might

appear in late adolescence. An approach to the evaluation of patients with CFTR-RD is seen in Figure 454.10.

TREATMENT

General Approach to Care

Initial efforts after diagnosis should be intensive and should include baseline assessment, initiation of treatment to prevent pulmonary involvement in young infants or reverse it in those diagnosed later, nutritional maintenance or remediation, and education of the patient and parents. Follow-up evaluations are scheduled every 1–3 months, depending on the age at diagnosis, because many aspects of the condition require careful monitoring. An interval history and physical examination should be obtained at each visit. 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 and physical exam and routine pulmonary function testing. Table 454.4 lists symptoms and signs that suggest the need for more intensive antibiotic and physical therapy (PT). Protection against exposure to MRSA, *P. aeruginosa*, *B. cepacian*, and other resistant gram-negative organisms is essential, including contact isolation procedures and careful attention to cleaning 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. Screening patients and caregivers for anxiety and depression annually is expected to identify issues that can interfere with adherence to daily care. 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 mucous clearance. Intravenous therapy for dehydration should be initiated early.

Table 454.4 Symptoms and Signs Associated with Exacerbation of Pulmonary Infection in Patients with Cystic Fibrosis

SYMPTOMS

Increased frequency and duration of cough
Increased sputum production
Change in appearance of sputum
Increased shortness of breath
Decreased exercise tolerance
Decreased appetite
Feeling of increased congestion in the chest

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

From Ramsey B. Management of pulmonary disease in patients with cystic fibrosis. *N Engl J Med.* 1996;335:179.

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 months. 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 complications is also an important part of management.

Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapies

CFTR modulator therapies are small molecules taken orally that correct the processing and function of the variant CFTR protein in multiple organs and reduce or correct manifestations of disease. They have been developed to target specific classes of pathogenic variants (see Fig. 454.2). Ivacaftor is a small-molecule potentiator of the CFTR pathogenic variant G551D (present in ~5% of patients). Ivacaftor activates the CFTR-G551D variant protein, a class III CFTR pathogenic variant that results in protein localized to the plasma membrane but loss of chloride channel function (Table 454.5; Fig. 454.11). Ivacaftor therapy results in improvement in FEV₁ by an average of 10.6%, decreases the frequency of pulmonary exacerbations by

Table 454.5 Cystic Fibrosis Transmembrane Regulator Modulators for Cystic Fibrosis

DRUG	FDA-APPROVED INDICATION	FORMULATIONS	USUAL DOSAGE
Ivacaftor	4 mo with a responsive pathogenic variant*	25, 50, 75 mg granule packets [†] 150 mg tablets	<6 yr: weight-based dosing [‡] ≥6 yr: 150 mg q12h
Lumacaftor/ivacaftor	≥2yr, F508del-homozygous	100/125, 200/125 mg tabs; 100/125, 150/188 mg granule packets [†]	6-11 yr: 200/250 mg q12h ≥12 yr: 400/250 mg q12h [§]
Tezacaftor/ivacaftor	≥6 yr, F508del-homozygous or F508del-heterozygous with another responsive pathogenic variant	Tablets: tezacaftor once per day and ivacaftor twice per day q12h	6-11 yr, <30 kg: AM: 50 mg tezacaftor + 75 mg ivacaftor PM: 75 mg ivacaftor 6-11 yr, ≥30 kg and 12 yr: AM: 100 mg tezacaftor + 150 mg tab ivacaftor PM: 150 mg tab ivacaftor
Elexacaftor/tezacaftor/ivacaftor	≥6 yr, one copy of F508del 2 yr - <6 yr, one copy of F508del	Tablets: 2 triple-combination tablets (orange) in AM and one ivacaftor tablet (blue) in PM ELX 80 or 100 mg TEZ 40 or 50 mg IVA 60 or 75 mg	6-11 yr, <30 kg: AM: elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg (2 combination tablets) PM: ivacaftor 75 mg 6-11 yr, ≥30 kg and 12 yr: AM: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (2 combination tablets) PM: ivacaftor 150 mg <14 kg: AM: ELX 80 / TEZ 40 AM and PM: IVA 60 ≥14 kg: AM: ELX 100 / TEZ 50 AM and PM: IVA 75

*Approved pathogenic variants: G551D, S549N, G1244E, G178R, S1251N, G551S, G1349D, S1255P, R117H, E56K, K1060T, P67L, E193K, A1067T, R74W, L206W, G1069R, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W, R117C, A455E, S977F, F1074L, F1052V, D115H; 3849 þ 10 kb C>T, 2789 þ 5G>A, 3273-26A>G, 711þ3A>G, E831X.

†The granules should be mixed with 5 mL of room-temperature or cold soft food or liquid and consumed within 1 hr.

‡In patients 4 mo to 6 yr old, the recommended dosage is 25 mg every 12 hr for weight 5 kg to <7 kg, 50 mg every 12 hr for those weighing <14 kg, and 75 mg every 12 hr for those weighing ≥14 kg.

§In patients 2-5 yr old, the recommended dosage is 100/125 mg every 12 hr for those weighing <14 kg and 150/188 mg every 12 hr for those weighing ≥14 kg.

||F508del heterozygotes with the following pathogenic variants: E56K, K1060T, P67L, E193K, A1067T, R74W, L206W, D110E, D110H, R347H, D579G, R1070Q, D1270N, R352Q, S945L, R1070W, R117C, A455E, S977F, F1074L, F1052V, D1152H, 3849þ10kb C>T, 2789 þ 5G>A, 3273-26A>G, 711þ3A>G.

Modified from The Medical Letter on Drugs and Therapeutics: Tezacaftor/Ivacaftor (Symdeko) for cystic fibrosis. *Med Lett.* 2018;60(1558):174-176, Table 3.

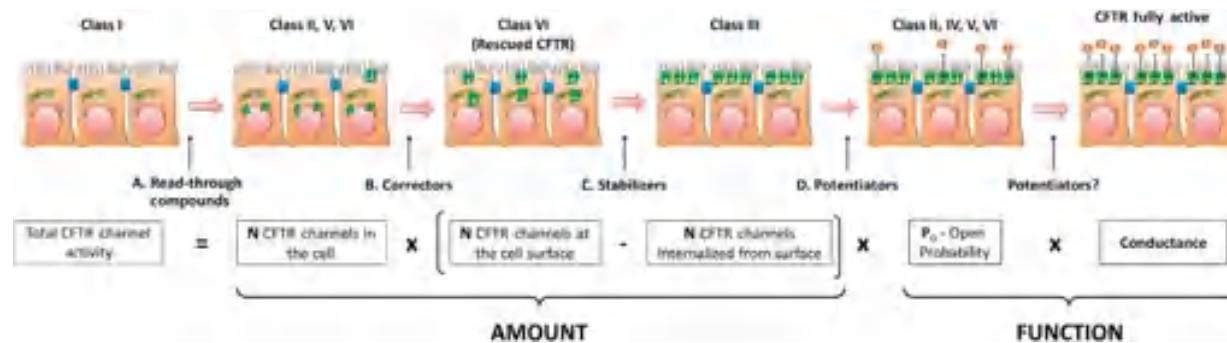


Fig. 454.11 Cystic fibrosis transmembrane conductance regulator (CFTR) pharmacologic modulators have different modes of action. A, Read-through compounds, which include aminoglycoside antibiotics (e.g., gentamicin, tobramycin), act by suppressing premature termination codons (PTCs), thus permitting translation to continue to the normal termination of the transcript and thus increasing the total amount of complete CFTR being produced in the cell. B, Correctors (e.g., VX-809, also known as lumacaftor; VX-661) potentially promote folding of variant CFTR protein, allowing it to escape ER degradation and reach the cell surface, thus increasing the number of channels present at the plasma membrane. C, Stabilizers include compounds (e.g., hepatocyte growth factor) that enhance CFTR retention/anchoring at the cell surface, thus also contributing to increase the number of channels present at the cell surface. D, Potentiators (e.g., VX-770, also known as ivacaftor) activate CFTR, that is, increase the open probability (P_o) of the channel by regulating its gating and possibly also the conductance. (From Bell SC, De Boeck K, Amaral MD. New pharmacological approaches for cystic fibrosis: promises, progress, pitfalls. *Pharmacol Therapeu*. 2015;145:19–34, Fig. 4.)

55%, decreases sweat chloride by an average of 48 mEq/L, and increases weight gain by an average of 2.7 kg. Ivacaftor is approved for patients older than 2 years of age with class III and class IV pathogenic variants.

The combination of ivacaftor with lumacaftor, a corrector that stabilizes misfolded F508del and enables trafficking of the variant molecule to the apical cell membrane where it is potentiated by ivacaftor, is available for patients older than 6 years of age who are homozygous for the F508del pathogenic variant (see Fig. 454.11). This medication is associated with smaller increments in pulmonary and nutritional outcomes but is an important proof-of-concept treatment.

Tezacaftor and ivacaftor is another combination indicated for patients ≥ 6 years with one or two Phe508del alleles. This combination improves predicted FEV₁ and overall well-being (see Table 454.5). VX-445 combined with tezacaftor-ivacaftor adds another CFTR correction agent; the triple combination improves predicted FEV₁ and reduces sweat chloride levels.

Elexacaftor/tezacaftor/ivacaftor, a triple combination therapy for patients ≥ 6 years with at least one copy of Phe508del alleles was approved in 2019 (see Table 454.5). This therapy is a highly effective modulator, and 90% of patients with CF are eligible to use this treatment. In a phase 3 randomized, double-blind trial for patients homozygous for Phe508del comparing elexacaftor/tezacaftor/ivacaftor to tezacaftor/ivacaftor alone, patients on triple therapy had a significant increase in FEV₁ percent predicted of 10% and a dramatic decrease in sweat chloride levels by 45 mM compared with double therapy at 4 weeks. In a phase 3 randomized, double-blind, placebo-controlled clinical trial for patients with one copy of Phe508del, triple therapy was associated with a decrease in sweat chloride by 41.8 mmol/L and a marked increase in FEV₁ percent predicted of 14% at 24 weeks. The success of these highly effective CFTR modulator therapies, ivacaftor for class III pathogenic variants and elexacaftor/tezacaftor/ivacaftor for Phe508del, has been life-changing. Ivacaftor and the triple combination therapy are being evaluated for therapeutic efficacy in younger children and infants with CF.

However, at least 10% of patients with CF have pathogenic variants that are not responsive to these highly effective modulator therapies. Patients with class I pathogenic variants caused by premature termination codons and failure to translate CFTR protein will require new approaches to therapy to acquire normal CFTR protein and function. Gene therapy, gene editing, and antisense oligonucleotide therapeutic approaches are currently being developed.

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

Human recombinant DNase (2.5 mg) enzymatically dissolves extracellular DNA released by neutrophils, a major contributor to the characteristically sticky and viscous CF airway secretions. Recombinant human DNase is usually given as a single daily aerosol dose; it improves pulmonary function, decreases the number of pulmonary exacerbations, and promotes a sense of well-being. Benefit for those with mild, moderate, and severe lung disease has been documented. Improvement is sustained for 12 months or longer with continuous therapy.

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. Seven percent hypertonic saline nebulized 2-4 times daily increases mucous clearance and reduces pulmonary exacerbation, with only a slight short-term improvement in pulmonary function.

Airway Clearance Therapy

Airway clearance treatment begins in infancy with chest percussion (with or without postural drainage) and derives its rationale from the idea that cough clears mucus from large airways, but chest vibrations are required to shear secretions from the airway wall and move secretions from small airways, where expiratory flow rates are low. Chest PT can be particularly useful for patients with CF because they accumulate secretions in small airways first, even before the onset of symptoms. Cessation of chest PT in children with mild to moderate airflow limitation results in deterioration of lung function within 3 weeks, and prompt improvement of function occurs when therapy is resumed, but it is less clear which available modality is best. Airway clearance therapy is recommended 2-4 times a day, depending on the severity of lung dysfunction, and usually increased during acute exacerbations. Cough, huffing, or forced expirations are encouraged intermittently throughout the session. Vest-type mechanical percussors (*high-frequency chest wall oscillation*) are commonly used past infancy because of their convenience, as are a variety of oscillatory positive expiratory pressure devices (such as Acapella and Aerobika) and other controlled breathing techniques (e.g., *autogenic drainage*). 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 can be shown to be superior to any other, so all modes should be considered in the development of an airway clearance prescription. Adherence to daily therapy is important but rarely achieved; 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

Table 454.6 Antimicrobial Agents for Cystic Fibrosis Lung Infection

ROUTE	ORGANISMS	AGENTS	DOSAGE (mg/kg/24 hr)	NO. DOSES/24 hr
Oral	<i>Staphylococcus aureus</i>	Dicloxacillin	25-50	4
		Linezolid	20	2
		Cephalexin	50	4
		Clindamycin	10-30	3-4
		Amoxicillin-clavulanate	25-45	2-3
	<i>Haemophilus influenzae</i>	Amoxicillin	50-100	2-3
	<i>Pseudomonas aeruginosa</i>	Ciprofloxacin	20-30	2-3
	<i>Burkholderia cepacia</i>	Trimethoprim-sulfamethoxazole	8-10*	2-4
	Empirical	Azithromycin	10, day 1; 5, days 2-5	1
		Erythromycin	30-50	3-4
Intravenous	<i>S. aureus</i>	Nafcillin	100-200	4-6
		Vancomycin	40	3-4
	<i>P. aeruginosa</i>	Tobramycin	8-12	1
		Amikacin	15-30	2-3
		Ticarcillin	400	4
		Piperacillin	300-400	4
		Ticarcillin-clavulanate	400†	4
		Piperacillin-tazobactam	240-400‡	3
		Meropenem	60-120	3
		Imipenem-cilastatin	45-100	3-4
		Ceftazidime	150	3
	<i>B. cepacia</i>	Aztreonam	150-200	4
		Chloramphenicol	50-100	4
		Meropenem	60-120	3
Aerosol		Tobramycin (inhaled)	300§	2
		Aztreonam (inhaled)	75	3

*Quantity of trimethoprim.

†Quantity of ticarcillin.

‡Quantity of piperacillin.

§In mg per dose.

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 one antibiotic to nearly continuous treatment with one 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, physical signs, or changes in pulmonary function testing or chest x-ray. Treatment is guided by identification of pathogenic organisms in respiratory tract cultures and *in vitro* sensitivity testing. Common organisms, including *S. aureus* (MRSA or methicillin-susceptible *S. aureus* [MSSA]), nontypeable *H. influenzae*, *P. aeruginosa*, *B. cepacia*, and other gram-negative rods, are encountered with increasing frequency. The usual course of therapy

is 2 weeks, and maximal doses are recommended. Table 454.6 lists useful oral antibiotics. The quinolones are the only broadly effective oral antibiotics for *Pseudomonas* infection, but resistance against these agents may emerge. 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

Aerosolized antibiotics are often used as part of daily therapy when the airways are infected with *P. aeruginosa*. Aerosolized tobramycin inhalation solution or powder, or aztreonam inhalation solution used as a suppressive therapy (on 1 month, off 1 month), may reduce symptoms, improve pulmonary function, and decrease the occurrence of pulmonary exacerbations. Although these therapies are sometimes used in acute pulmonary exacerbations, the evidence to support this application is limited.

Another important indication for aerosolized antibiotic therapy is to eradicate *P. aeruginosa* in the airways after initial detection. Early infection may be cleared for months to several years in this way, although eventual reinfection is common. Other antibiotics have been used via

inhalation, including liposomal amikacin and levofloxacin for *P. aeruginosa*, and there was no inferiority of efficacy compared with inhaled tobramycin.

Intravenous Antibiotic Therapy

For the patient who has not responded to oral antibiotics and intensive home measures with return of signs, symptoms, and FEV₁ to baseline, intravenous antibiotic therapy is indicated. This therapy is usually initiated in the hospital but is sometimes completed on an ambulatory basis if the likelihood of complete adherence to the therapeutic regimen is good. The ideal duration of treatment is unknown; although many patients show improvement within 7 days, many CF physicians believe that 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 454.6 lists commonly used intravenous antibiotics. In general, treatment of *Pseudomonas* infection is thought to require two-drug therapy. A third agent may be given for optimal coverage of *S. aureus* or other organisms. Aminoglycosides are usually effective when given every 24 hours to minimize toxicity and optimize convenience. Some CF physicians use peak and trough levels to guide dosing, but most clinical pharmacists recommend measuring levels at other times, commonly 2 and 12 hours, to use pharmacokinetic calculations to guide dosing. Changes in therapy should be guided by lack of improvement more than by culture results; sensitivities do not always predict response to therapy, and this may be because of the presence of other organisms that are not detected by culture methods. If patients do not show improvement, complications such as right heart failure; asthma; or infection with viruses, *A. fumigatus* (especially allergic bronchopulmonary aspergillosis, ABPA) (see Chapter 283), nontuberculous mycobacteria (see Chapter 263), or other unusual organisms should be considered. *B. cepacia* complex and *Acinetobacter* are 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 allergic bronchopulmonary aspergillosis. Reversible obstruction is conventionally defined as improvement of ≥12% in FEV₁ or FVC after inhalation of a bronchodilator. In many patients with CF, these may improve by only 5–10% (physiologic response), but subjects may report subjective benefit.

Antiinflammatory Agents

Corticosteroids are useful for the treatment of allergic bronchopulmonary aspergillosis and severe asthma occasionally encountered in children with CF. Prolonged systemic corticosteroid treatment of CF lung disease reduces the decline in lung function modestly but causes predictably prohibitive side effects. Inhaled corticosteroids have theoretical appeal, but there are contradictory and weak data regarding efficacy unless the patient has clinically diagnosable asthma. Ibuprofen, given chronically in high doses adjusted to achieve a peak serum concentration of 50–100 µg/mL, is associated with a slowing of disease progression, particularly in younger patients with mild lung disease. However, there are concerns regarding side effects of nonsteroidal antiinflammatory drugs, so this therapy has not gained broad acceptance. Macrolide antibiotics have an antiinflammatory effect, and 3 days/week of azithromycin has been shown to reduce the likelihood of the development of pulmonary exacerbations, especially in patients with chronic *Pseudomonas* airway infection, so this is a commonly used therapy.

Other Therapies

Attempts to clear recalcitrant atelectasis and airway plugging with bronchopulmonary lavage and direct instillation of various medications are sometimes used in exceptional cases; there is no evidence for sustained benefit from repeated procedures. 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 along with FEV₁.

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.

Hemoptysis

Endobronchial bleeding usually reflects airway wall erosion into hypertrophied bronchial vessels secondary to infection. Although more common in patients with advanced disease, it is sometimes seen in adolescents with relatively mild lung disease. Blood streaking of sputum is particularly common. Small-volume hemoptysis (<20 mL) is usually viewed as a need for intensified antimicrobial therapy and chest PT. **Massive hemoptysis**, defined as total blood loss of ≥250 mL in a 24-hr period, is rare in the first decade and occurs in <1% of adolescents, but it requires close monitoring and the capability to replace blood losses rapidly. Bronchoscopy rarely reveals the site of bleeding. Bronchial artery embolization can be useful to control persistent, significant hemoptysis.

Pneumothorax

Pneumothorax (see Chapter 461) is encountered uncommonly in children and teenagers with CF, although it may lead to significant compromise in lung function and occasionally 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. Video-assisted thoracoscopic surgery (VATS) 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. 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 or, most commonly, a decrease in FEV₁ that does not respond to antibiotic therapy (see Chapter 283). In some patients, a chest radiograph shows new focal infiltrates. A highly elevated total serum immunoglobulin E (IgE) level (>1,000) is usually the initial indication of the diagnosis. 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 IgE and IgG antibodies against *A. fumigatus*, or the presence of eosinophils in a fresh sputum sample supports the diagnosis. Treatment is directed at controlling the inflammatory reaction with oral corticosteroids. Oral antifungals are usually reserved for patients who relapse after initial steroid treatment. For refractory cases, omalizumab, humanized monoclonal anti-IgE, has been effective.

Nontuberculous Mycobacteria Infection

See Chapter 263.

Injured airways with poor clearance may be colonized by *M. avium*-complex but also *M. abscessus*, *Mycobacterium cheloneae*, 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. Infection with these organisms, or at least its recognition, has become increasingly

common. Treatment is prolonged and requires multiple antimicrobial agents. Symptoms may improve, but the nontuberculous mycobacteria are not usually cleared from the lungs.

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, especially in patients with advanced lung disease.

Acute Respiratory Failure

Acute respiratory failure (see Chapter 86) 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 PaO_2 . An increasing PCO_2 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. High-dose steroids have been anecdotally reported to be of benefit in this setting. Recovery is often slow. Intensive intravenous antibiotic therapy and postural drainage should be continued for 1-2 weeks 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 seen most frequently in adult patients. Because a long-standing $\text{PaO}_2 < 50 \text{ mm Hg}$ promotes the development of right-sided heart failure, patients usually benefit from low-flow oxygen to raise arterial Po_2 to $\geq 55 \text{ mm Hg}$. 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 pulmonary hypertension and cor pulmonale, and this complication should be treated. 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.

Pulmonary Hypertension and Cor Pulmonale

Individuals with long-standing, advanced pulmonary disease, especially those with severe hypoxemia ($\text{PaO}_2 < 50 \text{ mm Hg}$), often acquire pulmonary hypertension and chronic right-sided heart failure. Evidence for concomitant left ventricular dysfunction is often found. The arterial Po_2 should be maintained at $> 50 \text{ mm Hg}$, if possible, and hypercarbia corrected with noninvasive ventilation or intubation if necessary. Intensive pulmonary therapy, including intravenous antibiotics, is most important. Adjunctive therapy with salt restriction, diuretics, and pulmonary vasodilators may be indicated. The prognosis for heart failure is poor, but a number of patients survive for ≥ 5 years after the appearance of heart failure. Heart-lung transplantation may be an option.

Lung Transplantation

Lung transplantation is an option for end-stage lung disease (see Chapter 492). 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. Survival and quality of life after lung transplantation are better in patients with CF than other chronic lung diseases, probably because of the relatively younger age of recipients with CF, but the current estimated 5-year survival is about 50%, somewhat reduced compared with that of other solid organ transplants. Because of bronchiolitis obliterans (see Chapter 443.1) and other transplant-related 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 and duration of waits continue to be a problem. Importantly, since the initiation of treatment with elexacaftor/tezacaftor/ivacaftor, some patients with chronic lung disease have significantly improved so that they no longer require listing for lung transplantation.

Nutritional Therapy

Up to 90% of patients with CF have loss of exocrine pancreatic function leading to inadequate digestion and absorption of fats and proteins. They require dietary adjustment and augmentation, 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 has changed because of newborn screening, but even at 2-4 weeks, it is not uncommon to see that weight gain has begun to fall off the standard curve.

Most children with CF have a higher-than-normal caloric need because of malabsorption despite the use of pancreatic enzyme supplementation. Encouragement to eat high-calorie foods is important and often begins with more concentrated, high-calorie formulas in the first year. Even so, most mothers can breastfeed successfully. It is vitally important to promote adequate weight gain in the early years, both because of a clear relationship to later lung function and because early deficiencies make later catch-up growth more difficult. Not infrequently, feeding problems can negatively affect parent-child interactions at meal time, and behavioral interventions can improve caloric intake. The liberal use of appetite stimulants, especially cyproheptadine, in early childhood makes the struggle a bit easier. Poorly controlled lung disease increases metabolism and decreases appetite and needs to be considered when efforts to improve weight gain are unsuccessful.

Maintenance of good weight gain and body mass index in the first year of life leads to better long-term preservation of lung function, but there is a strong correlation between body mass index and FEV_1 that persists through all ages in people with CF. Better nutrition also leads to improved quality of life and psychologic well-being and provides better reserves when weight loss occurs in association with intermittent acute pulmonary exacerbations.

Malabsorption is an important contributor to nutritional deficiencies, and it is important to ensure that pancreatic enzyme dosing is adequate and consistently being taken correctly with all meals and feedings. Appetite stimulants when cyproheptadine is not successful may include megestrol, oxandrolone, dronabinol, antidepressants such as mirtazapine, and even growth hormone. CF-related diabetes needs to be ruled out.

When all these therapies fail, weight stabilization or gain can be achieved with nocturnal feeding via nasogastric tube or gastrostomy tube. These are most commonly resorted to in infants and adolescents, the two age-groups that have the most difficulty with weight gain because of high-normal demands.

Pancreatic Enzyme Replacement

Pancreatic exocrine replacement therapy given with ingested food reduces, but does not fully correct, stool fat and nitrogen losses. Current products are enteric-coated, pH-sensitive enzyme microspheres that come in capsules and are given to children before they can swallow by opening the capsule and mixing the beads in small amounts of acidic foods such as applesauce. Strengths ranging from 3 to 40,000 IU of lipase/capsule are available. Administration of excessive doses has been linked to fibrosing colonopathy and **colonic strictures**, so

recommendations are for enzyme dosing to stay below 2,500 lipase units/kg/meal in most circumstances. Snacks should also be covered. Some enzyme replacement therapies provide bicarbonate in addition to the enzymes, which may be helpful for a subset of patients to correct acid pH in the duodenum, which is caused by a lack of exocrine pancreatic secretions; neutralization of duodenal pH permits optimal activation of enteric-coated pancreatic exocrine replacement therapy granules. Some individuals prefer proton pump inhibitor therapy to achieve the same effect.

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 four vitamins for patients with CF are available. They should be taken daily. Despite this supplementation, vitamin D deficiency is common and should be treated with doses of cholecalciferol (vitamin D3) rather than ergocalciferol (vitamin D2). The CF Foundation recommends that all individuals with CF, from birth to 12 months of age, be treated with an initial dose of 400–500 IU vitamin D3 per day, from 12 months to 10 years of age, an initial dose of 800 to 1000 IU of vitamin D3 per day, and from 10 years of age and older, an initial dose of 800 to 2000 IU of vitamin D3 per day. Higher doses are recommended for those who are vitamin D deficient. Salt supplementation is also needed during infancy and is started at the time of diagnosis. There may be additional vitamin and micronutrient needs if a child with CF required an intestinal resection as a newborn as a result of meconium ileus.

TREATMENT OF INTESTINAL COMPLICATIONS

Meconium Ileus

When meconium ileus (see Chapter 135) is suspected, contrast enemas with reflux of contrast material into the ileum not only confirm the diagnosis but may also result in the passage of meconium and clearing of the obstruction. Children in whom this procedure fails require operative intervention. Children who have had meconium ileus are at greater risk for nutritional deficiency and are more likely to develop problems with DIOS when older. Infants with meconium ileus should be assumed to have CF unless proven otherwise.

Distal Intestinal Obstruction Syndrome and Other Causes of Abdominal Symptoms

Despite appropriate pancreatic enzyme replacement, a number 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 hydrators such as polyethylene glycol should be given. If this fails or symptoms are more severe, large-volume bowel lavage with a balanced salt solution containing polyethylene glycol may be taken by mouth or by nasogastric tube. When there is complete obstruction, a contrast enema, accompanied by large amounts of intravenous fluids, can be therapeutic.

Rectal Prolapse

See Chapter 392.5.

Although uncommon, rectal prolapse occurs most often in infants with CF and less frequently in older children with the disease. It was much more frequently seen in the past among undiagnosed young children with 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. To prevent an immediate recurrence, the buttocks can be temporally taped closed. Adequate pancreatic enzymes, stool softener, and control of pulmonary infection result in improvement. On very rare occasions, a patient may continue to have rectal prolapse and may require referral to a pediatric surgeon.

Hepatobiliary Disease

A wide range of hepatobiliary complications are observed in CF, including asymptomatic elevations in liver function tests, biliary cirrhosis, and portal hypertension. Often liver function abnormalities (elevations in aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT]) associated with biliary cirrhosis are

treated with ursodeoxycholic acid, leading to a reduction in these values. However, the evidence to support ursodeoxycholic acid's effectiveness in preventing the progression of CF-related liver disease has not been clearly documented. Portal hypertension with esophageal varices, hypersplenism, or ascites occurs in ≤8% of children with CF (see Chapter 415).

Obstructive jaundice in newborns with CF needs no specific therapy once the etiology has been established. End-stage liver disease is an indication for liver transplantation in children with CF (see Chapter 416).

Pancreatitis

Recurrent pancreatitis is seen primarily in patients with pancreatic sufficiency, and it can lead to the development of pancreatic insufficiency. Patients can be treated with pancreatic enzyme therapy and a low-fat diet (in well-nourished patients) to rest the pancreas. Further treatment of this disorder is discussed in Chapter 399.

Cystic Fibrosis-Related Hyperglycemia and Diabetes

Onset of hyperglycemia occurs most frequently *after* the first decade. Approximately 20% of young adults are treated for hyperglycemia, although the incidence of CF-related diabetes may be up to 50% in adults with CF. Ketoacidosis is rarely encountered. The pathogenesis includes both impaired insulin secretion and insulin resistance. Routine screening consisting of an annual 2-hour OGTT is recommended in children older than 10 years of age, although some cases may begin earlier. Although glucose intolerance with blood sugars that remain less than 200 are not treated unless nutrition is compromised or lung function seems affected, recent data suggest the prediabetic state is associated with clinical decline, so close monitoring is warranted. 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. When treatment is indicated, insulin should be instituted, as it is the only therapy shown to improve the nutritional and metabolic outcomes in CFRD. In addition to insulin therapy, patients are often encouraged to exercise, which has been shown to reduce post-prandial glycemic excursions. Medical nutritional therapy for CFRD differs from that recommended in type 1 diabetes and type 2 diabetes, as patients are encouraged to continue the nutritional therapy needed to manage CF, that is a higher-caloric diet that is high in fat and salt and not carbohydrate restricted. Strict carbohydrate counting with adjustments in insulin dosing is essential for good glycemic control. Patients with CFRD are at risk for microvascular complications, including retinopathy, nephropathy, and neuropathy, providing an additional rationale for good control of blood glucose levels. These long-term vascular complications of diabetes are more commonly observed in adults with CFRD, as they occur more commonly after a decade of the disease.

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 nonsteroidal 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 related to CFTR dysfunction.

OTHER COMPLICATIONS

Nasal Polyps

Nasal polyps (see Chapter 427) occur in 15–20% of patients with CF and are most prevalent in the second 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 universal in CF and 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 anecdotally 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, especially when thirsty in hot weather. Salt supplements are often prescribed to newborns and to children who live in hot weather climates. Hypochloremic alkalosis should be suspected in any patient who feels unwell in hot weather or who has had symptoms of gastroenteritis, and prompt fluid and electrolyte therapy should be instituted as needed.

Anxiety and Depression

The stress and emotional impact of caring for CF is significant. Studies have found high rates of depression and anxiety in both patients and their parent caregivers, 2-3 times that of the general population. Positive screening for depression in particular is associated with decreased lung function, lower body mass index, worse adherence, worse health-related quality of life, more frequent hospitalizations, and increased mortality. Annual screening for anxiety and depression, with psychologic and/or pharmacologic interventions and follow-up, is therefore indicated.

Surgery

Patients with good or excellent pulmonary status can tolerate general anesthesia without any intensive pulmonary measures before the procedure but should be adherent to their usual prescribed airway clearance therapy. Those with moderate or severe pulmonary infection usually do better with a 1- to 2-week 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. General anesthesia may provide an opportunity to perform bronchoscopy to evaluate the airway and obtain good cultures, and this should be considered in any child with CF who will undergo surgery for any indication.

After major surgery, cough should be encouraged, and airway clearance treatments should be reinstated as soon as possible, usually within 24 hours.

PROGNOSIS

CF remains a life-limiting disorder, although survival has dramatically improved (Figs. 454.12 and 454.13). With exceptions, most children remain relatively healthy into adolescence or adulthood. The slow progression of lung disease eventually does reach disabling proportions. Life table data indicate a median cumulative survival of more than 40 years, and the expectation is younger children with the disease have a life expectancy far in excess of this estimate. Outcomes are variable and related to CFTR pathogenic variant class, modifier genes, biologic and chemical exposures, disease management, and socioeconomic status. With the advent of highly effective CFTR modulator therapies, the landscape is expected to change even more dramatically. Not only will quality of life and longevity further improve, but investigations have begun into how the burden of care may be lessened by a decrease in the current dependence on onerous daily airway clearance therapies and the need for recurrent hospitalizations for pulmonary exacerbations.

Children with CF 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 years 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 the impact of anxiety and depression, dependence-independence issues, self-care, peer

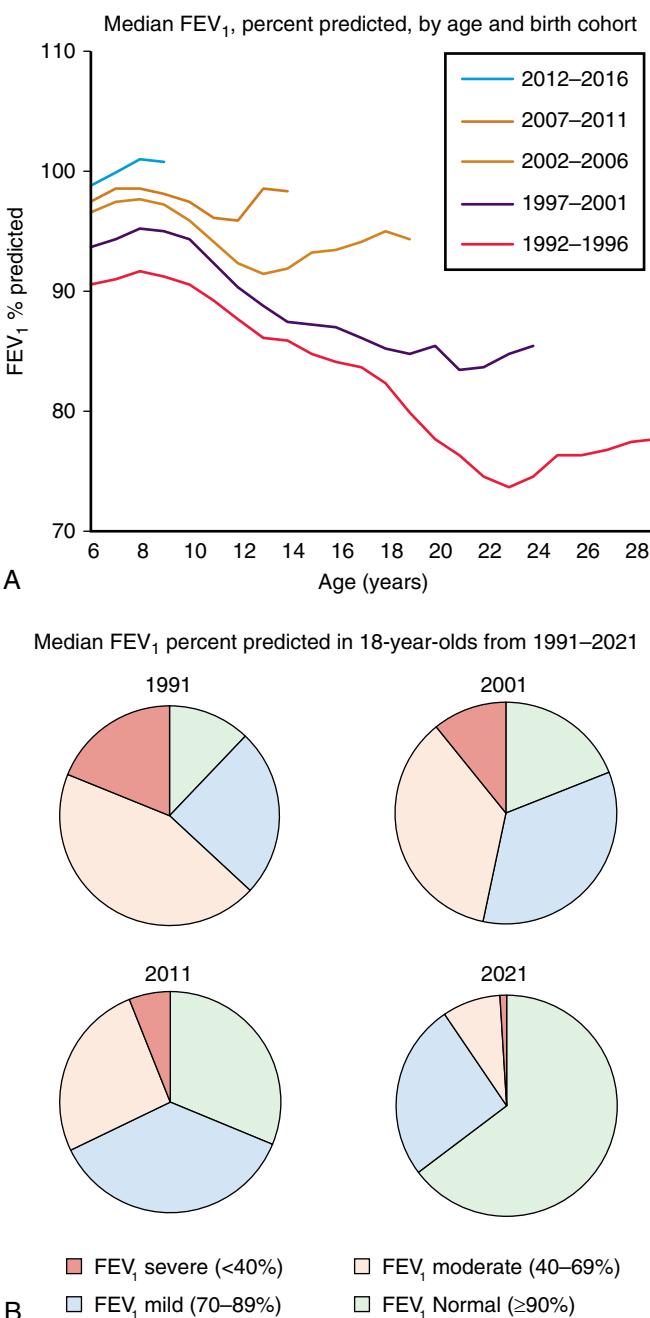


Fig. 454.12 Median FEV₁, percent predicted, by age and birth cohort (A), and in 18-yr-olds from 1991 to 2021 (B). (From the Cystic Fibrosis Patient Registry 2021. Annual Data Report. pp. 42–43. © 2022 Cystic Fibrosis Foundation. Bethesda, Maryland. <https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf>)

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.

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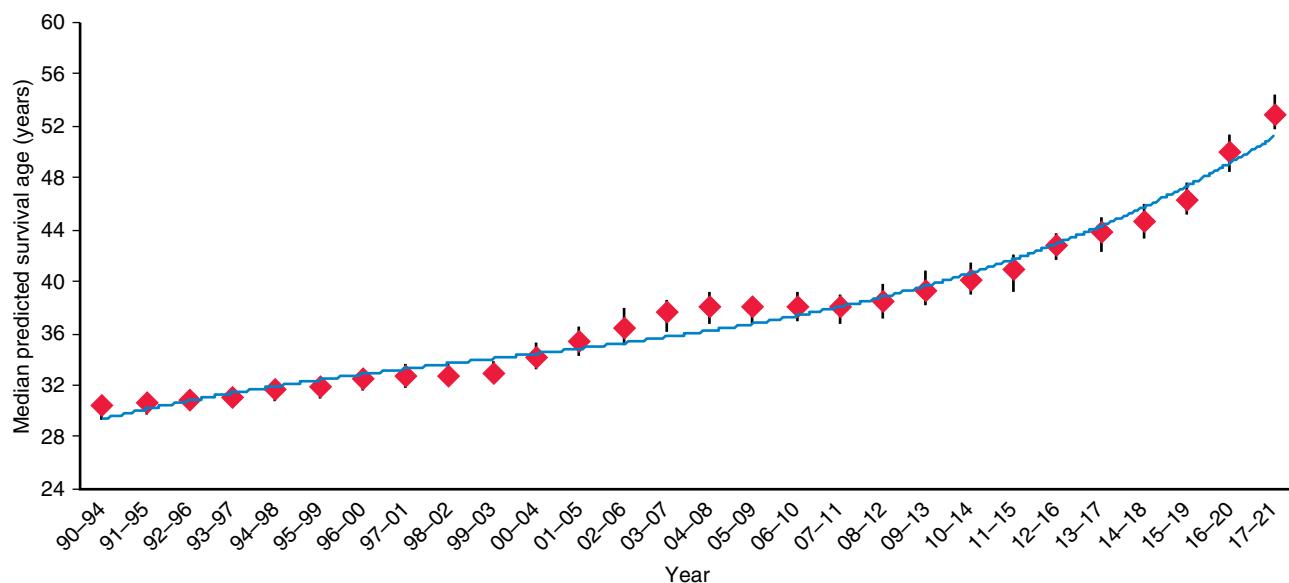


Fig. 454.13 Median predicted survival age, 1990–2021 in 5-yr increments. Created using the currently recommended method for calculating median predicted survival. For more information about the methodology, please see the Technical Supplement available at cff.org. (From the Cystic Fibrosis Patient Registry 2021. Annual Data Report. p. 70. © 2022 Cystic Fibrosis Foundation. Bethesda, Maryland. <https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf>)

Chapter 455

Primary Ciliary Dyskinesia (Immotile Cilia Syndrome, Kartagener Syndrome)

Thomas W. Ferkol Jr.

See also Chapter 101.3.

Primary ciliary dyskinesia (PCD) is an inherited disorder characterized by ciliary dysfunction leading to chronic sinopulmonary disease, persistent middle ear effusions, laterality defects, and infertility. The reported prevalence in the general population varies, ranging between 1 in 2,200 and 40,000 live births, but in children with repeated respiratory infections, it has been estimated to be as high as 5%.

NORMAL CILIARY ULTRASTRUCTURE AND FUNCTION

Three types of cilia exist in humans: motile cilia, primary (sensory) cilia, and nodal cilia. 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. A mature ciliated epithelial cell has approximately 200 uniform **motile cilia**, hairlike organelles that move fluids, mucus, and inhaled particulates vectorially from conducting airways (Fig. 455.1). Motile cilia 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. A cilium contains a central fibrillar structure, or axoneme, that consists of helical protofilaments made of alpha- and beta-tubulin monomers. A circular

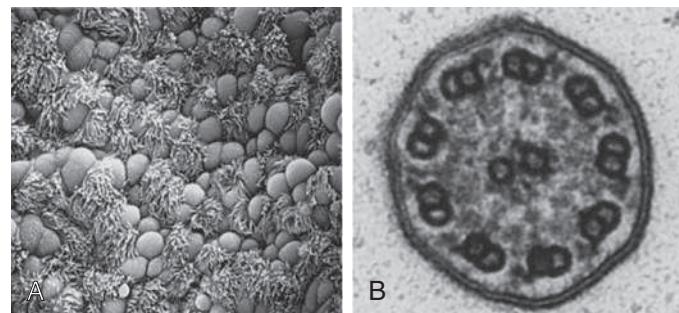


Fig. 455.1 Electron photomicrographs showing an airway epithelium grown in primary culture showing ciliated and nonciliated cells (A) and a normal motor cilium (B).

array of peripheral microtubular doublets are arranged around a central pair, leading to the characteristic “9+2” arrangement seen on cross-sectional views on transmission electron microscopy (see Fig. 455.1). Distinct inner and outer dynein arms are attached to the A microtubule. Each dynein arm is a multimer, containing multiple adenosine triphosphatases, called *dyneins*, that 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. The inner dynein arm and radial spokes are also parts of the dynein regulatory complex, a key regulator of motor activity. Nixin links connecting adjacent outer microtubular doublets limit the degree of sliding between microtubules. All these structures lead to synchronized ciliary beating, resulting in a ciliary stroke and coordinated beating at a frequency constant throughout the airway, ranging between 8 and 14 hertz, but this 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 wavelike 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 solitary, immotile organelles present during interphase on most cell types. These cilia lack a central microtubule doublet and dynein arms, thus creating a “9+0” arrangement (Fig. 455.2). Once considered nonfunctional vestigial remnants, primary cilia are important signaling organelles that sense the extracellular environment. They are mechanoreceptors, chemosensors, and osmosensors and, in specialized cases, detect changes in light, temperature, and gravity. Primary cilia defects (ciliopathies) 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 (see Chapter 101.3).

The third type of cilia exists only during a brief period of embryonic development. **Nodal cilia** have a “9+0” microtubule arrangement similar to that of primary cilia, but they exhibit a whirling, rotational movement (see Fig. 455.2), 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 ambiguus**, and **heterotaxy** associated with congenital heart disease, asplenia, and polysplenia (see Chapter 480.11).

GENETICS OF PRIMARY CILIARY DYSKINESIA

PCD is a genetically heterogeneous disorder, usually inherited by an autosomal recessive pattern, but autosomal dominant and X-linked inheritance are known. Pathogenic variants in any of the hundreds of proteins that are involved in ciliary assembly, structure, or function could theoretically cause disease. Indeed, 50 different genes have been linked to PCD (Fig. 455.3), including those that encode proteins integral to the outer dynein arm, dynein regulatory complex, radial spoke, and central apparatus proteins. Pathogenic variants in genes coding several cytoplasmic proteins not part of the cilia axoneme have also been identified, leading to defective protein transport and cilia assembly. Over 70% of all people with PCD tested have pathogenic variants in one of these genes. In addition, motile ciliopathies *distinct* from classical PCD have been described. Children with biallelic variants in *CCNO* and *MCIDAS*, two proteins required for centriole production, have oligocilia and clinical features similar to PCD.

Insights into the genetic bases of motile ciliopathies have also yielded greater understanding of genotype-phenotype relationships

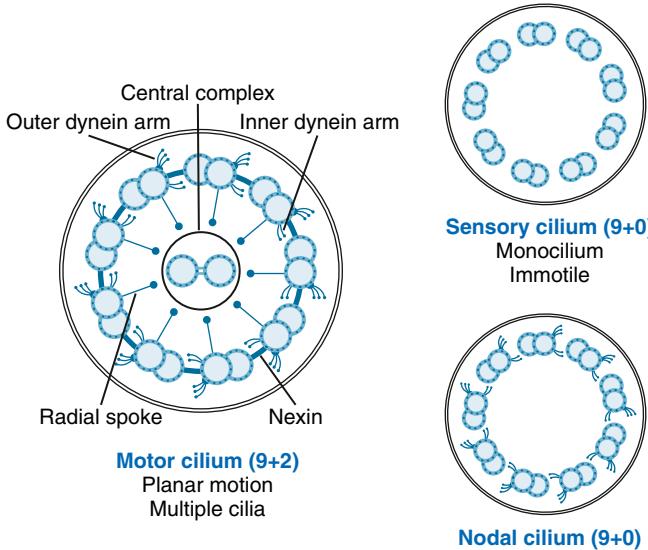


Fig. 455.2 Schemata showing the three general classes of normal cilia: motile cilia (motile “9+2”), nodal cilia (motile “9+0”), and primary cilia (nonmotile “9+0”), which demonstrate the complex structure and arrangement of the ciliary axoneme.

in PCD. For instance, cross-sectional and longitudinal studies showed that children with the inner dynein arm-microtubular disorganization defect, primarily the result of biallelic pathogenic variants in *CCDC39* or *CCDC40*, had more severe lung disease. In contrast, people with pathogenic variants in *RSPH1* appear to have milder respiratory phenotypes.

CLINICAL MANIFESTATIONS OF PRIMARY CILIARY DYSKINESIA

PCD has several characteristic clinical features (Table 455.1). **Neonatal respiratory distress** (NRD) is a common feature, and most affected term newborns develop increased work of breathing, tachypnea, and upper and middle lobe atelectasis on chest radiographs. The association of respiratory distress in *term neonates* with PCD has been underappreciated. Often diagnosed with transient tachypnea of the newborn or pneumonia, PCD infants frequently require supplemental oxygen flow for days to weeks.

Chronic, year-round productive (wet) cough that begins before 6 months of age is another characteristic feature of PCD. Bacterial cultures of sputum or lavage fluid frequently yield nontypeable *Haemophilus influenzae* (see Chapter 240), *Staphylococcus aureus* (see Chapter 227.1), *Streptococcus pneumoniae* (see Chapter 228), and *Pseudomonas aeruginosa* (see Chapter 251.1). Persistent airway infection and inflammation lead to **bronchiectasis**, even in preschool children (see Chapter 452). Children with PCD also have a higher prevalence of pectus excavatum and scoliosis.

Roughly 80% of patients with PCD have **chronic rhinosinusitis**, manifested by daily nasal congestion and copious, watery nasal

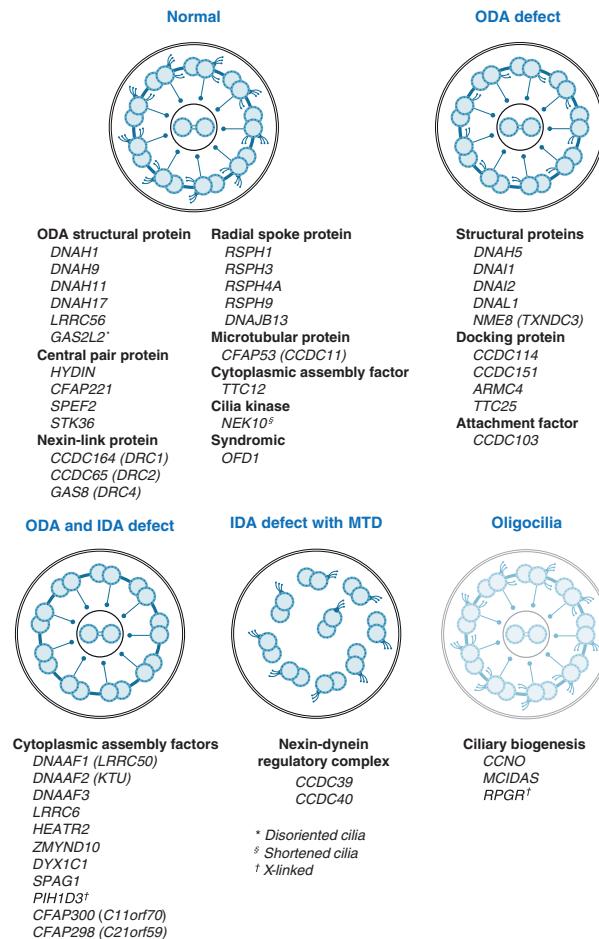


Fig. 455.3 Classification of genes associated with primary ciliary dyskinesia based on ultrastructural findings. IDA, Inner dynein arm; MTD, microtubular disorganization; ODA, outer dynein arm.

Table 455.1	Clinical Features of Primary Ciliary Dyskinesia
LOWER RESPIRATORY	
Unexplained respiratory distress in term neonate	
Daily productive (wet) cough since early infancy	
Chronic bronchitis	
Bronchiectasis	
UPPER RESPIRATORY	
Chronic otitis media and persistent middle ear effusions	
Conductive hearing loss	
Sensorineural hearing loss	
Daily nonseasonal rhinosinusitis since early infancy	
Chronic rhinosinusitis	
Nasal polypsis	
CARDIAC	
Situs inversus totalis	
Heterotaxy	
Congenital cardiac defects	
GENITOURINARY	
Male subfertility	
Female subfertility	
MUSCULOSKELETAL	
Pectus excavatum	
Scoliosis	
CENTRAL NERVOUS SYSTEM	
Retinitis pigmentosa	
Hydrocephalus (rare)	

discharge that begins early in infancy and persists into childhood. Inadequate innate mucous clearance leads to chronic sinusitis (see Chapter 429) and nasal polypsis. Middle ear disease occurs in many children with PCD, with varying degrees of **chronic otitis media with effusion**. Both conductive and sensorineural hearing loss occur at increased frequency in people with PCD, though the former is more common. Middle ear findings may be most helpful in distinguishing PCD from cystic fibrosis (CF) (see Chapter 454) or other causes of chronic lung disease.

Left-right laterality defects (e.g., *situs inversus totalis*) are found in ~50% of all children with PCD. Without functional nodal cilia in the embryonic period, thoracoabdominal orientation is random. Approximately 25% of children who have *situs inversus totalis* have PCD. Thus *situs inversus totalis* alone does not establish the diagnosis. Other laterality defects, such as **heterotaxy**, are also associated with PCD and may coexist with congenital cardiac defects, asplenia, or polysplenia. PCD should be strongly considered in term infants who have unexplained NRD and *situs anomalies*.

Most males with PCD have dysmotile spermatozoa because flagellar and ciliary ultrastructure is similar. Male infertility or subfertility is typical but not always found in this disease. Subfertility has also been reported in affected women, possibly related to 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.

Several conditions have overlapping features of motile and primary ciliopathies. X-linked retinitis pigmentosa has been associated with recurrent respiratory infections in families with *RPGR* gene pathogenic variants. Intraflagellar transport proteins are essential for photoreceptor assembly and, when mutated, lead to apoptosis of the retinal pigment epithelium (see Chapter 670).

Table 455.2	Consensus-Based Primary Ciliary Dyskinesia (PCD) Diagnostic Criteria by Age
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NEWBORNS (0-1 MO OF AGE)

Situs inversus totalis and unexplained neonatal respiratory distress (NRD) at term birth, plus at least one of the following:

- Diagnostic ciliary ultrastructure on electron micrographs
- Two pathogenic variants in PCD-associated gene

CHILDREN (1 MO TO 5 YR)

Two or more major PCD clinical criteria (NRD,* daily wet cough, persistent nasal congestion, laterality defect), plus at least one of the following (nasal nitric oxide not included in this age-group because it is not yet sufficiently tested):

- Diagnostic ciliary ultrastructure on electron micrographs
- Two pathogenic variants in one PCD-associated gene
- Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy on multiple occasions

CHILDREN (5-18 YR OF AGE) AND ADULTS

Two or more PCD clinical criteria (NRD,* daily productive cough or bronchiectasis, persistent nasal congestion, laterality defect), plus at least one of the following:

- Nasal nitric oxide during plateau <77 nL/min on two occasions, >2 mo apart (with CF excluded)
- Diagnostic ciliary ultrastructure on electron micrographs
- Two pathogenic variants in one PCD-associated gene
- Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy on multiple occasions

*In term neonates.

DIAGNOSIS OF PRIMARY CILIARY DYSKINESIA

The diagnosis of PCD has been challenging. A high index of suspicion is necessary, but pediatricians should only perform testing in children who have clinical manifestations consistent with the disease. PCD has four criteria-defined features that should be used to screen at-risk children: unexplained NRD in full-term infants, left-right laterality defects, persistent rhinitis that begins before 6 months of age, and daily wet or productive cough that also starts before 6 months of age (Table 455.2). Even though chronic otitis media is common in PCD, many unaffected infants and toddlers also have chronic middle ear involvement, which makes this feature less useful in distinguishing children with PCD from others.

Imaging studies show extensive involvement of the paranasal sinuses. Chest radiographs frequently demonstrate bilateral lung overinflation, peribronchial infiltrates, and lobar atelectasis. Computed x-ray tomography of the chest often reveals bronchiectasis, often involving the anatomic right middle lobe or lingula, 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 50% of people with the condition. Pulmonary function tests may be normal early but demonstrate obstructive airway disease as the disease progresses. Typical findings include decreased forced expiratory volume in 1 second (FEV_1), reduced expiratory flow rates, and increased residual volume. Bronchodilator responsiveness is variable. Longitudinal analyses of children with PCD show wide variation in intrathoracic airway obstruction.

No single test will diagnose every person with PCD. Historically, transmission electron microscopy has been the gold standard to assess structural defects within the cilium. These ultrastructural defects are found in cilia throughout the upper and lower airways and oviduct and in sperm flagella. Curettage from the nasal epithelium or endobronchial brushing can provide an adequate specimen for review. Identification of a specific, previously established defect in the ciliary structure with concurrent phenotypic features is sufficient to make the diagnosis. There are several characteristic ciliary abnormalities: outer dynein arm defects, combined inner and outer dynein arm defects, and inner

dynein arm defects with microtubular disorganization (see Fig. 455.3). Inner dynein arm defects alone are largely artifactual. It is important to note that ultrastructural examination of cilia as a diagnostic test for PCD has limitations. First, the absence of axonemal defects does not exclude PCD; nearly 30% of affected individuals have normal ciliary ultrastructure. Other children with symptoms consistent with PCD have been found to have ciliary aplasia or few motile cilia on the epithelial surface (see Fig. 455.3).

Careful interpretation of the ultrastructural findings is necessary because ciliary defects can be acquired. Nonspecific changes (e.g., compound cilia or blebs) may be seen in relation to exposure to environmental pollutants or infection. Frequently, the diagnosis of PCD can be delayed or missed because of inadequate tissue collection or sample processing or misinterpretation of ciliary defects. Some investigators have advocated culturing of airway epithelial cells and allowing the secondary changes to resolve. Alternatively, immunofluorescent staining for axonemal protein markers may overcome some limitations of transmission electron microscopy.

Another useful approach has exploited the observation that nasal nitric oxide concentrations are reduced in subjects with PCD. Because nasal nitric oxide measurements are relatively easy to perform and non-invasive, this method is a valuable screen for PCD. When compared to other diagnostic tools, nasal nitric oxide can be sensitive and specific for PCD in cooperative older children and adults. Unfortunately, few studies in children under 5 years have been reported, and the accuracy of nasal nitric oxide measurements in infants has not been established. It is important to note that children who have pathogenic variants in some PCD-associated genes can have nondiagnostic nasal nitric oxide concentrations. Conversely, people with CF (see Chapter 454) or primary immunodeficiencies (see Chapter 165), conditions that have clinical features that overlap with PCD, can have reduced nasal nitric oxide levels. Thus reduced nasal nitric oxide concentrations alone are never sufficient to make the diagnosis of PCD.

Qualitative tests to assess ciliary function have been used to screen for PCD. Ciliary beat frequency measurements using standard light microscopy have been used as a screen, but this approach can be misleading and should never be used as a diagnostic tool. High-resolution, high-speed digital imaging of ciliary motion in multiple planes permits comprehensive analysis of cilia beating, which has shown that certain beat patterns are associated with specific ultrastructural defects. This technique is available only at specialized centers, primarily in Europe, and requires sophisticated software and expertise.

PCD is highly heterogeneous owing to the large number of proteins involved in cilia assembly, structure, and function. Advances in gene sequencing techniques have led to the identification of a growing number of disease-associated genes. Genetic testing has become increasingly available and is considered a first-line test for PCD, incorporated into published diagnostic algorithms. Nevertheless, current, commercially available testing for pathogenic variants in at least 30 genes will only identify approximately 70% of affected children (see Fig. 455.3).

TREATMENT

No therapies have been shown to correct ciliary dysfunction in PCD. Many of the treatments applied to children with the condition are similar to those used in other chronic suppurative lung diseases characterized by impaired airway clearance and bronchiectasis, such as CF (see Chapter 454), but few have been adequately studied to demonstrate efficacy in PCD.

Strategies to enhance mucociliary clearance are central to PCD therapy, and routine airway clearance techniques using postural drainage, percussion vests, positive expiratory pressure devices, or other techniques should be instituted daily. Because ciliary function is impaired, cough becomes a critical mechanism for mucous clearance and should not be suppressed. Exercise can enhance airway clearance in people

with PCD and should be encouraged. Inhaled hypertonic saline and mucolytic agents are often used in CF care, but only small case series or single-site clinical trials showed any improvement in people with PCD after treatment. Thrice-weekly azithromycin as an antiinflammatory agent is reported to reduce the frequency of pulmonary exacerbations but has no effect on lung function or quality-of-life measures.

When children with PCD develop increasing respiratory symptoms consistent with infection, antimicrobial therapy should be instituted based on respiratory culture results and bacterial sensitivities. Maintenance therapy with inhaled or oral antibiotics can be used cautiously in patients with PCD who have bronchiectasis or frequent respiratory exacerbations. Immunizations against pertussis, influenza, and pneumococci are cornerstones of care. Additional preventive measures include avoidance of cigarette or marijuana smoke, electronic cigarette aerosols, and other airway irritants.

Rarely, surgical resection of bronchiectatic lung has been performed on people with PCD, typically in cases of localized disease with severe hemoptysis or intractable infections. 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 people with PCD. Adults have undergone successful heart-lung, double-lung, or living-donor lobar lung transplantation. Situs inversus totalis complicates the procedure because of anatomic considerations. Otherwise, survival is similar to that for other transplant recipients.

Treatment of chronic otitis media and middle ear effusions in people with PCD is controversial. Myringotomy tubes are frequently placed in affected children, and some studies reported enhanced hearing in children with chronic conductive hearing loss after the procedure. However, others did not find improvement in hearing acuity. Intractable mucoid otorrhea, tympanosclerosis, and permanent membrane perforation are known complications of myringotomy tubes in people with PCD, leading some to recommend against surgical management. Although hearing tends to improve with time, children and adolescents with PCD 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, but 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 patients with PCD. It is believed that progression and extent of lung disease can be slowed with early diagnosis and therapy. Routine surveillance studies recommended the following for the care of children with PCD: (1) regular spirometry to monitor pulmonary function, (2) chest imaging, and (3) sputum or oropharyngeal cultures to assess respiratory flora.

Children with PCD usually have a slower decline in pulmonary function than those with CF, and its prognosis and long-term survival are better. Many can have a normal or near-normal life span, whereas others experience progressive bronchiectasis and respiratory deterioration at a younger age.

Chapter 456

Diffuse Lung Diseases in Childhood

See also Chapter 448.

456.1 Inherited Disorders of Surfactant Metabolism

Jennifer A. Wambach, Lawrence M. Nogee,
Aaron Hamvas, and F. Sessions Cole III

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 characterized: 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 pulmonary surfactant. The adenosine triphosphate-binding cassette protein member A3, ABCA3, is a transporter located on the limiting membrane of lamellar bodies, the intracellular storage organelle for surfactant within AEC2s, 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 one gene for SP-D (*SFTP D*) 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 recognized in humans and are collectively termed **surfactant dysfunction disorders** (Table 456.1). Variants in *SFTP D* have not been associated with disease, and pathogenic variants in the genes encoding SP-A have only been found in adults with idiopathic pulmonary fibrosis or lung cancer.

PATHOLOGY

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) and 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. Because the prognosis and inheritance patterns differ depending on the gene involved, genetic testing should be offered when one of these conditions is reported in the lung biopsy or autopsy of an infant or child. Other disorders, including genetic causes of **pulmonary alveolar proteinosis** (see Chapter 456.2), and disorders of immune dysregulation can be associated with similar pathologies.

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 126) but typically affects full-term infants. The initial degree of respiratory distress is variable, but the disease is progressive and is refractory to

Table 456.1 Comparison of Surfactant Dysfunction Disorders

	SP-B DEFICIENCY	SP-C DISEASE	ABCA3 DEFICIENCY	TTF-1 DISORDERS
Gene name	<i>SFTPB</i>	<i>SFTPC</i>	<i>ABCA3</i>	<i>NKX2-1</i>
Age of onset	Birth	Birth to adulthood	Birth to childhood; rarely adult	Birth to childhood
Inheritance	Recessive	Dominant/sporadic	Recessive	Sporadic/dominant
Mechanism	Loss of function	Gain in toxic function or dominant negative	Loss of function	Loss of function Gain in function
Natural history	Lethal	Variable	Generally lethal, may be chronic	Variable
DIAGNOSIS				
Biochemical (tracheal aspirate)	Absence of SP-B and presence of incompletely processed proSP-C	None	None	None
Genetic (DNA)	Sequence <i>SFTPB</i>	Sequence <i>SFTPC</i>	Sequence <i>ABCA3</i> ; copy number variant detection	Sequence <i>NKX2-1</i> ; copy number variant detection
Ultrastructural (lung biopsy-electron microscopy)	Disorganized lamellar bodies	Not specific; may have dense aggregates	Small dense lamellar bodies with eccentrically placed dense cores	Variable
Treatment	Lung transplantation or compassionate care	Supportive care, lung transplantation if progressing	Lung transplantation or compassionate care for infants with biallelic null variants; lung transplantation for other variants if progressing	Supportive care; treat coexisting conditions (hypothyroidism)

SP, Surfactant protein.

mechanical ventilation, surfactant replacement therapy, and glucocorticoid administration. Almost all affected infants have died without lung transplantation, but prolonged survival is possible in cases of partial deficiency of SP-B. Humans heterozygous for loss-of-function variants in *SFTPB* are clinically healthy 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 variants in *SFTPB* have been identified. The most common is a net two base-pair insertion in codon 133 (originally termed *121ins2*, currently termed *c.397delCinsGAA, p.Pro133Glufs*95*) that results in a frameshift, an unstable SP-B messenger RNA (mRNA) transcript, and absence of SP-B protein production. This pathogenic variant has accounted for 60–70% of the alleles found to date in infants identified with SP-B deficiency and is present in approximately 0.07% of European-descent individuals in large-scale sequencing projects. Most other pathogenic variants have been family-specific. A large deletion encompassing two exons of *SFTPB* has also been reported.

Diagnosis

A rapid, definitive diagnosis can be established with sequence analysis of *SFTPB*, which is available through clinical laboratories (Genetic Testing Registry, <https://www.ncbi.nlm.nih.gov/gtr>). Sequencing of *SFTPB* is usually performed as part of a multigene panel using next-generation sequencing (NGS) methods that includes genes for other surfactant dysfunction disorders and can be designed to detect deletions or duplications of one or more exons (copy number variants). For families in which *SFTPB* variants were previously identified, antenatal diagnosis can be established by preimplantation genetic diagnosis (PGD) or molecular assays of DNA from chorionic villous biopsy or amniocytes, which permit advanced planning of a therapeutic regimen. Other laboratory tests remain investigational, including analysis of tracheal aspirate (effluent) for the presence or absence of SP-B protein and for incompletely processed precursor proSP-C peptides that have been identified in SP-B-deficient human infants. 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 infant 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-ASSOCIATED INTERSTITIAL LUNG DISEASE (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. The mature SP-C protein (35 amino acids) is derived from proteolytic processing of a larger precursor protein (proSP-C).

Clinical Manifestations

The clinical presentation of patients with *SFTPC* pathogenic variants 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 findings of **interstitial lung disease**, or as **pulmonary fibrosis** in the fifth or sixth decade of life. The age and severity of disease vary even within families with the same *SFTPC* variant. The natural history is also quite variable, with some patients improving either spontaneously or as the result of therapy or prolonged mechanical ventilation, some with persistent respiratory insufficiency, and some progressing to

the point of requiring lung transplantation. This variability in presentation, severity, and course of the disease does not appear to correlate with the specific *SFTPC* variant and also hinders accurate assessment of prognosis.

Genetics

Multiple pathogenic variants in *SFTPC* have been identified in association with acute and chronic lung disease in patients ranging in age from newborn to adult. A pathogenic variant on only *one SFTPC* allele is sufficient to cause disease. Approximately half of these variants arise spontaneously, resulting in sporadic disease, but the remainder are inherited as a *dominant trait*. *SFTPC* pathogenic variants have been identified in diverse racial and ethnic groups. A threonine substitution for isoleucine in codon 73 (termed *p.I73T* or *p.Ile73Thr*) has accounted for 25–35% of the cases identified to date but is rare (not identified in gnomAD in ~140,000 individuals). Pathogenic variants in *SFTPC* are thought to cause disease because of a toxic gain in function resulting from the production of misfolded or abnormal proSP-C that accumulates within the AEC2 and causes cellular injury or alters the normal intracellular routing of proSP-C. Lung tissue from individuals with pathogenic variants in *SFTPC* demonstrates accumulation of pro-SPC. Many pathogenic *SFTPC* variants are located in the carboxy-terminal domain of pro-SP-C, which has a similar homology to other members of the BRICHOS family of membrane proteins, the abnormal aggregation of which have been implicated in the pathophysiology of familial dementia and some cancers. Pathogenic variants within the BRICHOS domain (amino acid residues 90–197) of *SFTPC* result in aggregation of misfolded protein in the endoplasmic reticulum, activation of the unfolded protein response, inflammation, and subsequent fibrosis. Non-BRICHOS domain pathogenic variants result in mistrafficking of pro-SPC to the plasma membrane and endosomes rather than the lamellar bodies, a late block in macroautophagy, inflammation, and subsequent fibrosis. The different underlying pathogenic mechanisms of *SFTPC* variants do not appear to correlate with the clinical presentation and may necessitate different therapeutic approaches.

Diagnosis

Sequencing of *SFTPC*, the only definitive diagnostic test, is available usually as part of an NGS multiple-gene panel in clinical laboratories. Because most *SFTPC* pathogenic variants are missense variants, distinguishing true disease-causing variants 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 PATHOGENIC VARIANTS IN ABCA3 (SURFACTANT METABOLISM DYSFUNCTION, PULMONARY, 3; SMDP3; OMIM #610921)

Clinical Manifestations

Lung disease caused by pathogenic variants 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 first year of life with **interstitial lung disease** similar to SP-C-associated interstitial lung disease. Infants who are homozygous or compound heterozygous for null variants, that is, the variant is predicted to result in the absence of protein expression (i.e., nonsense or frameshift variants), typically present with lethal neonatal respiratory failure, whereas infants with missense, in-frame insertion/deletions or splicing variants have more variable age of onset and outcomes. Heterozygosity for an *ABCA3* variant may contribute to the risk for RDS in late preterm and term infants, who, in contrast to *ABCA3*-deficient infants with variants on both alleles, may eventually completely recover from their initial lung disease.

Genetics

Recessive variants in *ABCA3* were first described among infants who presented with lethal RDS 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 400 variants

scattered throughout the gene have been identified, most of which are family-specific. The presence of null variants on both alleles that are predicted to preclude any ABCA3 production has been associated with early-onset disease and a uniformly fatal prognosis without lung transplant. A missense variant that results in a valine substitution for glutamine in codon 292 (p.Glu292Val or p.E292V) in association with a second ABCA3 variant has been found in children with severe neonatal respiratory failure and in older children with interstitial lung disease and is present in approximately 0.7% of European-descent individuals. ABCA3 variants have been identified in diverse racial and ethnic groups. The precise frequency of disease is unknown; large-scale sequencing projects indicate that the overall carrier rate for ABCA3 variants may be as high as 1 in 50 to 1 in 70 individuals. However, many ABCA3 variants are private, have not been previously identified in affected individuals, and functional data are only available for a limited number of disease-associated variants, thereby limiting these estimates. Two mechanistic classes of ABCA3 variants have been identified: those that disrupt intracellular trafficking of ABCA3 to the lamellar bodies with retention of the variant protein in the endoplasmic reticulum and those that traffic normally but impair adenosine triphosphate (ATP)-mediated phospholipid transport into the lamellar bodies. ABCA3 deficiency may 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, usually as part of an NGS multiple-gene panel, 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 variants may exist in untranslated regions that are not generally analyzed. As large deletions spanning one or more exons have been identified, it is important that the gene panel be able to detect such variants. In situations when the sequence analysis results are inconclusive, 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 pathogenic variants. 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 PATHOGENIC VARIANTS IN NKX2-1 (THYROID TRANSCRIPTION FACTOR 1, CHOREOATHETOSIS, 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*. Multiple large deletions involving the NKX2-1 locus and contiguous genes as well as missense, frameshift, nonsense, and small insertion or deletion variants 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 three organ systems has been referred to as **brain-thyroid-lung syndrome**, but disease may manifest in only one or two 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 NKX2-1 transcriptionally regulated proteins. No clear genotype-phenotype correlations have emerged, but children harboring complete gene deletions have generally had more severe and earlier-onset disease. This observation could also be related to the deletion of other adjacent genes. Although limited data are available, the pulmonary phenotype may depend on 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 collectin expression are more likely to have chronic lung disease.

Genetics

The NKX2-1 gene is small, spanning less than 3,000 bases, with only three exons. TTF-1 is expressed not only in the lung but also in the thyroid gland and 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, club cell secretory protein, and many others. Two transcripts that differ depending on whether the transcriptional start site is in the first or second exon have been recognized, although the shorter transcript is the predominant transcript in the lung. Most NKX2-1 pathogenic variants 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. Loss-of-function variants in NKX2-1 are rare in large sequencing projects, but the prevalence of disease is unknown. Pathogenic variants in diverse ethnic groups have been recognized. Most reported variants 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, usually as part of an NGS multiple-gene panel, and is the preferred method for diagnosis. Because large deletions comprise a significant fraction of reported variant alleles, specific methods to assess for deletions should also be performed, such as a chromosomal microarray or gene-targeted deletion/duplication analysis. A pathogenic variant on one allele is sufficient to cause disease. Although isolated pulmonary disease has been recognized, the majority of reported affected individuals have manifestations in two 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 thyroxine (T₄) and high thyroid-stimulating hormone levels. The lung pathology associated with NKX2-1 pathogenic variants 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 one 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 first year of life. Conventional neonatal intensive care interventions can maintain extrapulmonary organ function for a limited time (weeks to several 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 pathogenic variants 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 (Fig. 456.1). Infants with severe and progressive respiratory failure attributable to ABCA3 deficiency may be candidates

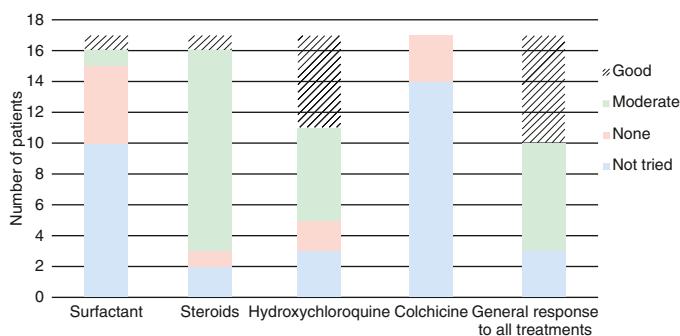


Fig. 456.1 Response to therapies for 17 patients with *SFTPC* variants. (Data from Kröner C, Reu S, Teusch V, et al. Genotype alone does not predict the clinical course of *SFTPC* deficiency in paediatric patients. Eur Respir J. 2015;46:197–206.)

for lung transplantation. The variable natural history of patients with *SFTPC* variants 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 *NKX2-1* variants is largely supportive. Hypothyroidism, if present, should be treated with thyroid hormone replacement. Corticosteroids and other agents used for other types of surfactant dysfunction have not been formally evaluated. Some individuals have progressive lung disease and have undergone lung transplantation. 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 to inform recurrence risk for future pregnancies, to present antenatal diagnostic options and offer delivery at a center with neonatal intensive care, and to facilitate discussions regarding whether testing should be offered to other family members who may not be symptomatic.

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456.2 Pulmonary Alveolar Proteinosis

Jennifer A. Wambach, Lawrence M. Nogee,
F. Sessions Cole III, and Aaron Hamvas

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by the intraalveolar and terminal airway accumulation of surfactant leading to progressive hypoxic respiratory failure. PAP can result from abnormalities in surfactant production or surfactant clearance. Histopathologic examination shows distal air spaces are 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 the primary mechanism for its accumulation is impaired catabolism by alveolar macrophages. PAP is classified as either *primary* due to disruption of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling or *secondary* due to several different diseases that reduce alveolar macrophage number or function (Table 456.2). A fulminant, usually lethal, form of PAP 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 (see Chapter 456.1).

Etiology and Pathophysiology

Primary Alveolar Proteinosis

Disordered signaling of 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. Variants in the genes encoding both the α and β subunits of the GM-CSF receptor (*CSF2RA*, *CSFR2B*) in children with PAP account for a genetic basis for some cases of primary PAP in childhood.

Secondary Alveolar Proteinosis

Alveolar proteinosis has also been reported in children, including young infants, with **lysine-rich protein intolerance**, a rare autosomal recessive disorder caused by pathogenic variants in the cationic amino acid transporter *SLC7A7* (see Chapter 105.14). These children generally present with vomiting, hyperammonemia, and failure to thrive, although their pulmonary disease may prove fatal. A case of *recurrence* of the disease after lung transplantation supports a primary role for alveolar macrophage dysfunction in the pathogenesis of PAP associated with lysine-rich protein intolerance. PAP is also a prominent feature in patients with biallelic variants in the gene encoding methionyl tRNA synthetase (*MARS*), who have a multiorgan phenotype that also includes liver disease as a prominent feature and is prevalent among individuals on Reunion Island. The mechanism for PAP in patients with *MARS* variants is unknown. Heterozygous variants in the gene encoding the transcription factor *GATA2* have also been associated with a phenotype that includes PAP, as well as immune deficiencies, myelodysplasia, and lymphatic abnormalities. The mechanism for PAP in patients with such variants likely is related to the role of *GATA2* in alveolar macrophage development. Heterozygous gain-in-function variants in the *OAS1* gene have been identified in infants and children with a phenotype that includes PAP, hypogammaglobulinemia, and immune dysfunction. *OAS1* gene products are important in the innate immune response to viral infection, and gene activation leads to inhibition of protein synthesis and apoptosis, with apoptosis of alveolar macrophages likely resulting in PAP. PAP may also be associated with some subtypes of Niemann-Pick disease (see Chapter 106.4).

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; hematologic disorders (myelodysplastic syndrome); and nonhematologic malignancies 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, and males are affected three times as often as females.

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. Immunohistochemical 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 for diagnosis 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

Table 456.2 Comparison of Pulmonary Alveolar Proteinosis Syndromes

	AUTO-IMMUNE	GM-CSF RECEPTOR DEFICIENCY	LYSINURIC PROTEIN INTOLERANCE	MARS DEFICIENCY	GATA2 DEFICIENCY	OAS1-ASSOCIATED POLYMORPHIC AUTOINFLAMMATORY IMMUNO-DEFICIENCY
Gene(s)		CSFR2A, CSFR2B	SLC7A7	MARS	GATA2	OAS1
Age of onset	Adult > child	Childhood to adult	Childhood	Childhood to adult	Childhood to adult	Infancy
Inheritance	NA	Recessive	Recessive	Recessive	Sporadic/dominant	Sporadic/dominant
Mechanism	Neutralizing antibodies to GM-CSF	Loss of function	Loss of function	Loss of function	Loss of function; haploinsufficiency	Gain in function
Other manifestations			Emesis; failure to thrive	Liver disease; hypothyroidism	Immune deficiency; myelodysplasia	Systemic inflammation, including fever, dermatitis, diarrhea, leukocytosis, splenomegaly
DIAGNOSIS						
Biochemical	Detection of serum GM-CSF autoantibody	Elevated serum GM-CSF levels	Increased cationic amino acids in urine, especially lysine	None	None	Hypogammaglobulinemia
Genetic (DNA)	NA	Sequence CSFR2A, CSFR2B	Sequence SLC7A7	Sequence MARS	Sequence GATA2	Sequence OAS1
Treatment	Whole lung lavage; inhaled GM-CSF	Whole lung lavage; hematopoietic stem cell transplantation	Whole lung lavage, dietary protein restriction, administration of citrulline and nitrogen scavenging drugs	Whole lung lavage	Whole lung lavage; hematopoietic stem cell transplantation	Whole lung lavage, intravenous immunoglobulin (IVIG), hematopoietic stem cell transplantation

GM-CSF, Granulocyte-macrophage colony-stimulating factor.

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 remission of PAP in adults and remains a therapeutic option for patients with childhood PAP (Fig. 456.2). 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 with inhaled recombinant GM-CSF (molgramostim) has been reported in adults with autoimmune-mediated PAP. Because children with GM-CSF receptor defects generally have high serum levels of GM-CSF, exogenous GM-CSF seems unlikely to be effective in most such cases. Depending on the nature of the variant(s) responsible for the deficiency, some responsiveness of the receptor may be retained such that a response to exogenous GM-CSF is possible. Because 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.

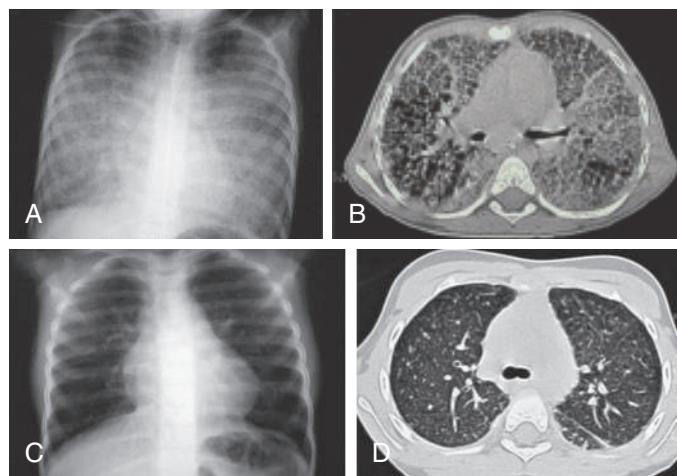


Fig. 456.2 A and B, Severe pulmonary alveolar proteinosis in a 5-year-old child before therapeutic lung lavage. A, Chest radiograph shows diffuse alveolar and interstitial infiltrates. B, CT scan demonstrates major air space opacities and crazy-paving pattern. C and D, Same patient after 12 therapeutic lung lavages. C, Chest radiograph demonstrates improvement of alveolointerstitial infiltrates. D, CT scan shows regression of the air space opacities with a residual micronodular pattern. (From De Blic J. Pulmonary alveolar proteinosis in children. *Paediatr Respir Rev*. 2004;5:316–322.)

Chapter 457

Pulmonary Hemosiderosis

Mary A. Nevin

Pulmonary hemorrhage may be characterized as focal or diffuse based on the location(s) of bleeding (see Chapter 458.2). The diagnosis of pulmonary hemosiderosis refers to the subset of patients with **diffuse alveolar hemorrhage (DAH)**. Bleeding in DAH occurs as a result of injury to the microvasculature of the lung and may be slow and insidious because of the low-pressure pulmonary circulation. Pulmonary hemosiderosis has classically been characterized by the triad of iron-deficiency anemia, hemoptysis, and radiographic evidence of alveolar infiltration. However, many of those affected, particularly young patients, are likely to present atypically, and a high index of suspicion for this condition must be maintained. Pulmonary hemosiderosis can exist in isolation, but more commonly occurs in association with an underlying condition. Defining a precise etiology for hemorrhage may be elusive. A diagnosis of **idiopathic pulmonary hemosiderosis (IPH)** is made when DAH occurs in isolation and an exhaustive evaluation for an underlying pathologic etiology is found to be unrevealing or nondiagnostic.

ETIOLOGY

The pathogenesis of pulmonary hemosiderosis is diverse, but DAH may be classified based on histopathologic examination. Three histopathologic patterns have been described: pulmonary capillaritis, bland pulmonary hemorrhage, and diffuse alveolar damage. Of these, pulmonary capillaritis is most frequently encountered and appears to carry a negative prognosis in those affected with DAH.

The histopathologic finding of **pulmonary capillaritis** is characterized by neutrophilic inflammation of the alveolar interstitium, endothelial edema, and fibrinoid necrosis. DAH with pulmonary capillaritis is frequently associated with an underlying systemic vasculitic process or collagen vascular disease.

Disorders associated with pulmonary capillaritis include systemic lupus erythematosus (SLE; see Chapter 199), drug-induced capillaritis, anti-glomerular basement membrane (GBM) antibody syndrome (Goodpasture syndrome), IgA vasculitis (Henoch-Schönlein purpura) (see Chapter 210), and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, including granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyangiitis (MPA; see Chapter 210), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Additional etiologies of pulmonary capillaritis include primary antiphospholipid antibody syndrome, rheumatoid arthritis, hypocomplementemic urticarial vasculitis, and acute lung transplant rejection. DAH in individuals with ANCA-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) is frequently associated with pathologic evidence of pulmonary capillaritis. In patients with Goodpasture syndrome, antiphospholipid syndrome, and SLE, DAH has been reported with pathologic evidence of capillaritis, but bland hemorrhage has also been described. Isolated pulmonary capillaritis may also be seen in the absence of ANCA positivity.

Drugs, including propylthiouracil, aspirin, hydralazine, and tumor necrosis factor alpha (TNF- α) antagonists, have been implicated as an etiology for pulmonary capillaritis and DAH. Finally, alveolar hemorrhage with capillaritis has been increasingly described as a complication of hematopoietic cell transplantation.

Pulmonary hemosiderosis with the histopathologic finding of **bland hemorrhage** is found when there is an absence of alveolar capillary inflammation or endothelial and cellular disruption. Both anti-GBM disease and SLE may be associated with bland hemorrhage, although

the finding of capillaritis is more typical. Other causes of bland hemorrhage include cardiac or cardiopulmonary derangements (pulmonary hypertension, mitral stenosis, mitral regurgitation, arteriovenous malformation), disseminated intravascular coagulation (DIC), coagulopathies, and anticoagulant therapy. Bland hemorrhage is also described in IPH.

Diffuse alveolar damage (DAD) is characterized by diffuse alveolar and interstitial edema with hyaline membrane formation. It is the pathognomonic finding in acute respiratory distress syndrome (ARDS) and is seen with a variety of infections, including opportunistic pathogens in immunocompromised individuals. Drug toxicity (sirolimus, nitrofurantoin, amphetamines, vaping), radiation therapy, and pulmonary embolus and infarction are other described etiologies for DAD with pulmonary hemorrhage. Table 457.1 provides a summary and classification of the diagnoses that may manifest with recurrent or chronic pulmonary hemorrhage.

EPIDEMIOLOGY

Disorders that present as DAH are highly variable in their severity and in their associated symptomatology and identifiable

Table 457.1 Diffuse Alveolar Hemorrhage Syndromes

DISORDERS WITH PULMONARY CAPILLARITIS

- Granulomatosis with polyangiitis (Wegener granulomatosis)
- Microscopic polyangiitis
- Systemic lupus erythematosus (SLE)
- Systemic sclerosis
- Polymyositis
- Anti-GBM antibody syndrome (Goodpasture)
- Antiphospholipid antibody syndrome
- IgA vasculitis (Henoch-Schönlein purpura)
- Hypocomplementemic urticarial vasculitis
- Rheumatoid arthritis
- Immunoglobulin A nephropathy
- Behcet syndrome
- Cryoglobulinemia
- Endocarditis
- Drug-induced capillaritis (retinoic acid, propylthiouracil, etanercept, infliximab, hydralazine)
- Idiopathic pulmonary-renal syndrome
- Acute lung transplant rejection
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- Hematopoietic cell transplantation

DISORDERS WITH BLAND HEMORRHAGE

- Anti-GBM antibody syndrome (Goodpasture)
- Systemic lupus erythematosus (SLE)
- Idiopathic pulmonary hemosiderosis
- Heiner syndrome
- Acute idiopathic pulmonary hemorrhage of infancy
- Thrombocytopenia syndromes (ITP, TTP)
- Hemolytic uremic syndrome
- Mitral stenosis
- Celiac disease (Lane-Hamilton syndrome)
- Nonaccidental trauma
- Drugs (anticoagulation, toxins)

DISORDERS WITH DIFFUSE ALVEOLAR DAMAGE

- Systemic lupus erythematosus (SLE)
- Polymyositis
- Immunodeficiency and opportunistic infection
- Pulmonary infarction
- Radiation therapy
- Acute respiratory distress syndrome (ARDS)
- Pulmonary hypertension
- Pulmonary edema
- Drugs (amphetamines, propylthiouracil, penicillamine, vaping)

Modified from Susarla SC, Fan LL. Diffuse alveolar hemorrhage syndromes in children. *Curr Opin Pediatr*. 2007;19:314–320.

abnormalities in laboratory testing; the diagnosis may be significantly delayed, making frequency estimates unreliable. Similarly, the prevalence of IPH is largely unknown. Of children and young adults diagnosed with IPH in the past, it has been postulated that 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 to 1.23 cases per million. Children and adolescents have traditionally accounted for 30% of cases. The ratio of affected males:females is 1:1 in the childhood diagnosis group, and males are only slightly more affected in the group diagnosed as young adults. In pediatric and adolescents undergoing allogeneic hematopoietic cell transplantation, pulmonary hemorrhage has been described in 2% of the population.

PATHOLOGY

DAH has been associated with diffuse inflammation, cytokine activation, and autoimmune responses. Elevations of both ferritin and interleukin (IL)-6 have been described as key factors in the exaggerated inflammatory response seen in pulmonary hemorrhage. 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) 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. The presence of persistent blood in three bronchoalveolar lavage (BAL) specimens from the same lobe is highly suggestive of the diagnosis. **Hemosiderin-laden macrophages (HLMs)** are seen with recovering, recurrent, or chronic pulmonary hemorrhage and are identifiable both in BAL fluid and in pathologic specimens of lung tissue. Approximately 48 hours is necessary 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, goblet 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 (see Chapter 448.3). 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 ANCAAs may be helpful in diagnosis and management, but the clinician must be aware that other ANCA-positive vasculitides, such as MPA and **eosinophilic granulomatosis with polyangiitis**, may share this nonspecific laboratory finding. In small vessel vasculitides, ANCAAs cause an inflammatory reaction that results in injury to the microvasculature. Antiproteinase-3 antibodies (cANCAAs) are classically associated with granulomatosis with polyangiitis, whereas antimyeloperoxidase antibodies (pANCAAs) are typically found in patients with MPA.

Patients with MPA (previously the microscopic variant of polyarteritis nodosa) demonstrate a systemic necrotizing vasculitis with a

predisposition 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.

Anti-GBM antibody syndrome (Goodpasture disease) is an immune complex-mediated disease in which anti-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 a relatively uncommon complication in SLE, its occurrence is often severe and potentially life-threatening; mortality rates exceed 50% in some cohorts, and early recognition is crucial to allow timely implementation of immunomodulatory therapies.

In **IgA vasculitis (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 intraalveolar 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, anti-GBM antibody syndrome, SLE, and MPA. As Henoch-Schönlein purpura may also have renal involvement, it has been suggested for inclusion as a pulmonary renal syndrome.

Pulmonary Hemorrhage in Infancy

An infant's neonatal course may be complicated by pulmonary hemorrhage. The most common diagnoses in infants with DAH are congenital heart disease (including pulmonary hypertension) and prematurity. Additional diagnostic considerations in an infant with pulmonary hemorrhage include congenital or acquired lung disease (congenital diaphragmatic hernia, sepsis), congenital or acquired coagulopathies (extracorporeal membrane oxygenation [ECMO], liver failure), and infection. Pulmonary hemorrhage in infants may be unrecognized if the volume of blood is insufficient to reach the proximal airways. Even with more significant blood loss, the tussive force of an infant may be insufficient to produce hemoptysis. Because the radiographic findings in pulmonary hemorrhage may be appreciated instead as a worsening picture of respiratory distress syndrome, edema, or infection, a high index of suspicion is required.

Acute Idiopathic Pulmonary Hemorrhage of Infancy

In 1994 and 1997, case reports suggested clusters of infantile pulmonary hemorrhage in association with environmental exposure to *Stachybotrys chartarum*. A review by the Centers for Disease Control and Prevention did not support an association between exposure to the mold and infantile pulmonary hemorrhage. Acute idiopathic pulmonary hemorrhage of infancy (AIPHI) has been defined as pulmonary hemorrhage in a previously healthy infant who is less than 1 year of age and born at a gestational age of greater than 32 weeks. Three criteria must simultaneously be met; these include (1) the sudden onset of bleeding or "frank" evidence of blood in the airway; (2) severe presentation leading to respiratory distress or failure and resulting in hospitalization in intensive care with intubation and mechanical ventilation; and (3) diffuse bilateral pulmonary infiltrates found on chest radiographs or computerized tomographic imaging. AIPHI is believed to be a rare diagnosis, and an exhaustive search for an identifiable etiology of pulmonary hemorrhage is advocated.

Pulmonary hemosiderosis in association with non-IgE-mediated cow's milk hypersensitivity is characterized by variable and

reversible (with elimination of cow's milk protein) symptoms of milk intolerance in infants and young children. Symptoms can include grossly bloody or occult heme-positive stools, vomiting, failure to thrive, gastroesophageal reflux, upper airway congestion, and iron-deficiency anemia. Association with pulmonary hemorrhage has remained controversial, but multiple case series have provided support for the anecdotal association.

A number of case reports and case series have suggested an association between **celiac disease** (see Chapter 384) 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 may be warranted.

DAH has been described in association with numerous other conditions. These are typically noninflammatory in nature and may be diversely attributable to cardiac, vascular, lymphatic, or hematologic etiologies. DAH has also rarely been attributed to nonaccidental trauma.

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 hemoptysis 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 hemoptysis. Because 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 ventilatory derangements, 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. In particular, young infants and children with DAH may come to attention with entirely nonspecific and nonpulmonary symptomatology such as failure to thrive or jaundice.

Primary or reported symptoms may reflect an underlying and associated disease process or comorbid condition. 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.

LABORATORY FINDINGS AND DIAGNOSIS

Bronchoscopic evaluation is an important tool in the diagnosis of pulmonary hemosiderosis. The yield is highest if performed within the first 48–72 hours after an acute hemorrhage. Cultures should be sent for bacterial, viral, fungal, and mycobacterial pathogens.

In addition, the evaluation of BAL fluid with silver stain for pneumocystis is advocated. When the pulmonologist recovers persistent or worsening blood with repeated BAL of the same lung segment, the diagnosis of DAH is supported. The presence of greater than 20% HLMs in BAL fluid is considered diagnostic. In the absence of bronchoscopy, sputum or pulmonary secretions should be analyzed for significant evidence of blood or HLMs and may provide supportive evidence in a patient who is able to adequately expectorate secretions from the lower airway. Gastric secretions may also reveal HLMs.

Pulmonary hemorrhage is classically associated with a microcytic, hypochromic anemia. Reduced serum iron levels, a decreased or normal total iron-binding capacity, and normal to increased ferritin levels may be found with chronic disease. 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 hemorrhage.

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, anti-double-stranded DNA, rheumatoid factor, antiphospholipid antibody (APL), myeloperoxidase, lupus anticoagulant, anticardiolipin antibody, and anti-GBM antibody evaluates for a number of immune-mediated and vasculitic processes that may be associated with pulmonary capillaritis.

Chest x-rays may reveal evidence of acute or chronic disease. Hyperaeration is frequently seen, especially during an acute hemorrhage. Infiltrates are typically symmetric and may spare the apices of the lung. Atelectasis may be appreciated. With chronic disease, fibrosis, lymphadenopathy, and nodularity may be seen. High-resolution CT imaging may reveal diffuse ground-glass opacification and alveolar opacification. With large bleeds, a fluid collection may be appreciated.

The presence of a cardiac murmur, cardiomegaly on x-ray, or a clinical suspicion of congenital or acquired heart disease suggests the need for a complete cardiac evaluation, including electrocardiogram and echocardiogram.

Pulmonary function tests generally reveal obstructive lung 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, serologic evidence of vasculitis, or circulating GBM antibodies. When surgically obtained, pulmonary tissue should be evaluated for evidence of immune complex deposition, inflammatory change in the pulmonary vascular bed, and granulomatous disease. Transbronchial biopsy is not generally recommended, as the lung involvement in DAH is frequently nonhomogeneous and "patchy" in character.

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 BAL, 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 may be recommended in an effort to guide therapy or determine prognosis in an individual with DAH of unknown etiology.

TREATMENT

Supportive therapy, including volume resuscitation, ventilatory support, supplemental oxygen, and transfusion of blood products, may be warranted in the patient presenting acutely with pulmonary hemorrhage. In the presence of ARDS, high oxygen concentrations and high positive end-expiratory pressure (PEEP) may be required. Surgical or medical therapy should be directed at any treatable underlying condition. High-dose systemic corticosteroids are frequently used as first-line treatment and are expected to be of particular benefit in the setting of immune-mediated disease. Steroids inhibit the acute inflammatory response (neutrophil influx, cytokine storm) associated with hemorrhage and may decrease progression toward fibrotic disease. High-dose steroids may contribute to morbidity and mortality in patients who have an infectious etiology for their hemorrhage and in those who are immunocompromised. A thorough evaluation for immunocompetence and pan-cultures for infectious organisms are therefore strongly advocated.

Medication dosing may vary with regard to primary diagnosis, age, comorbidities, and other factors. Clinical-pharmacologic correlation is advocated. Low- to moderate-dose treatment regimens may be provided in the form of methylprednisolone 2-4 mg/kg/day divided every 6-12 hours or in the form of prednisone 0.5-1 mg/kg daily and decreased to every other day after resolution of acute symptoms. High-dose corticosteroid therapy generally uses 10-30 mg/kg/day of IV methylprednisolone for 3-5 days and is followed by a tapering dose over 4-6 weeks. 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 hour for 3-5 consecutive days and repeated weekly or monthly. Early treatment with corticosteroids appears to decrease episodes of hemorrhage, but high doses of steroids carry the risk of renal disease, immunosuppression, and potentially fatal infections.

A variety of steroid-sparing and alternative immunosuppressive agents, including cyclophosphamide, Cytoxan, azathioprine, hydroxychloroquine, methotrexate, 6-mercaptopurine, and IVIG, have all been used successfully as adjunctive therapy in patients with severe, chronic, unremitting, or recurrent hemorrhage.

Plasmapheresis is a recognized adjunctive therapy for DAH with pulmonary capillaritis in ANCA-associated vasculitis, SLE, and anti-GBM antibody disease. Pheresis is generally performed daily or every other day for 14 days. In each plasma exchange, the total volume of plasma is replaced with fresh-frozen plasma (FFP) or albumin. In recent analyses, the long-term efficacy of plasmapheresis as compared with corticosteroid therapy has been questioned. At this time, treatment guidelines suggest the use of plasmapheresis in patients with ANCA-associated vasculitis who are critically ill with hypoxemic respiratory failure.

Rituximab has evolved as an additional adjunctive therapeutic option. It is a monoclonal antibody that targets CD-20 and has been found to be an effective option for individuals with connective tissue and autoimmune disorders.

Any coagulopathic disorders should be corrected in an effort to achieve hemostasis. Cryoprecipitates, FFP, and platelets may be transfused depending on the identified deficiency. Vitamin K may also be supplemented.

Prothrombotic factors, including antifibrinolytics such as tranexamic acid (TXA), thrombin, and factor VIIa, have been used in the treatment of DAH. TXA acts by preventing the conversion of plasminogen into plasmin and hinders fibrinolysis. Inhalational TXA has been associated with favorable treatment outcomes in children with DAH. TXA has been described as being less efficacious in those with hematologic malignancies and those individuals with massive or recurrent bleeding. Further study is indicated to define associated risk and populations expected to benefit most consistently from this therapy.

Recombinant factor VIIa (FVIIa) may be used in an effort to achieve hemostasis in those with massive hemorrhage. A therapeutic response to low doses of FVIIa has been reported with direct intrapulmonary instillation, but the use of this agent is still anecdotal outside of hemophilia. Factor VIIa appears to decrease the requirement for transfusions and to be an effective adjunctive therapy for critically ill children with massive hemorrhage. The efficacy of FVIIa in neonates and infants less than 1 year of age is yet to be established.

In the most critically ill children, additional life-sustaining interventions may be required; ECMO combined with immunosuppression was reported to be successful in allowing recovery from a severe hemorrhage with hypoxic respiratory failure in the setting of pANCA-positive MPA. In neonatal and infantile pulmonary hemorrhage, clinical improvement in blood gas and ventilatory requirements have been described with intrapulmonary administration of exogenous surfactant.

The potential adverse effects of these pharmacologic and therapeutic interventions should be recognized, and treated patients must be closely monitored for drug-related complications. Cushing syndrome, systemic hypertension, diabetes, and immunodeficiency are well-recognized complications 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.

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 multideterminant; underlying disease process, recurrence patterns, severity of hemorrhage, and delays in presentation are recognized prognostic factors. 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 generally attributable to massive hemorrhage or, alternatively, to progressive fibrosis, respiratory insufficiency, and right-sided heart failure.

The 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 years. Subsequent reviews have demonstrated vastly improved 5-year (86%) and 8-year (93%) survival in association with the use of immunosuppressive therapies. In IPH, the presence of hypoxia at clinical presentation and a positive antinuclear antibody have been demonstrated to be risk factors for recurrence.

Chapter 458

Pulmonary Embolism, Infarction, and Hemorrhage

458.1 Pulmonary Embolus and Infarction

Mary A. Nevin

Venous thromboembolism (VTE) is a term that describes both deep venous thrombosis (DVT) and pulmonary embolism (PE). PE is defined as obstruction of a pulmonary artery, typically as a result of thrombus formation. Although VTE remains relatively rare in occurrence, these events have become recognized as increasingly prevalent clinical problems and are associated with significant morbidity and mortality in the pediatric population. An increased incidence of VTE has been described in infants, children, and adolescents; this has been attributed to multiple factors, including increased survival from previously fatal critical and chronic illnesses, the increased use of central venous catheters, and improved diagnostic tools. Pulmonary emboli are more likely to be silent or to present atypically in infants and children as compared to adults, and a delay in diagnosis is commonly encountered. A diagnosis of PE may only be discovered on postmortem examination. In a retrospective study of PE found at the time of autopsy, the investigators discovered antemortem consideration of the diagnosis in only 15% of cases. Although children are more likely than their adult counterparts to have one or more predisposing factors favoring VTE (Table 458.1), a PE is often the first presenting symptom, and a high index of suspicion is needed to allow timely and accurate recognition as well as optimal management of PE in children.

Etiology

In the adult population, PE and VTE may be idiopathic in ~30% of patients. Children with DVT and PE are much more likely to have one or more identifiable conditions or circumstances placing them at risk. At least one identifiable risk factor for PE and VTE has been found in ≥80% of affected children. Most children have multiple and coexisting risk factors. In the pediatric population, the most common risk factors for VTE include the presence of an indwelling central venous catheter, congenital heart disease or vascular anomalies, trauma, immobility, recent surgery, malignancy, congenital and acquired thrombophilia, obesity and pregnancy, or hormonal drug therapies, including oral contraceptives. Individuals with nephrotic syndrome, inflammatory bowel disease, systemic lupus erythematosus, and sickle cell disease are also recognized as being at increased risk for thromboembolic disease. Both SARS-CoV-2/COVID-19 infection and the COVID-19-associated multisystem inflammatory syndrome in children (MIS-C) have been associated with a hypercoagulable state and increased risk for VTE, particularly in children and young adults who are critically ill with respiratory complications.

Although an embolus can also consist of air, septic material, amniotic fluid, or neoplastic tissue, emboli most commonly originate from thrombus formation. The most common risk factor for VTE in children is the presence of a central venous catheter (CVC); these indwelling lines are used for long-term administration of chemotherapy, antibiotics, and parenteral nutrition. The presence of a catheter in a vessel lumen, as well as instilled medications, can induce endothelial damage and favor thrombus formation. The use of a CVC is associated with ~90% of recognized VTE in neonates and ~30–60% of VTE in children. Septic emboli are rare in children but have been seen in osteomyelitis, endocarditis, Lemierre syndrome, and individuals with cellulitis.

Children with malignancy are recognized as being at high risk for VTE. Thromboembolic disease has been described in 7–16% of those with soft tissue sarcoma and in 5.2% of individuals with acute lymphocytic leukemia

(ALL). A child with malignancy may have numerous risk factors that relate to both the primary disease process and therapeutic interventions. Infection related to chronic immunosuppression, indwelling catheters, and the hypercoagulable state of malignancy itself are additional factors that favor VTE. Chemotherapeutic agents such as L-asparaginase have been implicated as conferring risk for VTE. In addition, steroids may contribute to the risk of VTE by increasing factor VIII. In a retrospective cohort of patients with VTE, pediatric malignancy was the chronic medical condition most strongly associated with recurrent VTE.

In the neonatal period, VTE is frequently associated with the presence of an indwelling CVC. Comorbid medical conditions often confer additional risk for thromboembolic disease in the neonate; the most common associated diagnoses are congenital heart disease and sepsis. Another known contributor is the relative immaturity of newborn infant coagulation; plasma concentrations of vitamin K-dependent coagulation factors (II, VII, IX, X); factors XII, XI, and pre-kallikrein and high molecular weight kininogen are physiologically lower in neonates and children (see Chapter 524). Infants with congenitally acquired homozygous deficiencies of antithrombin, protein C, and protein S may also present with thromboembolic disease in the neonatal period. Testing for these acquired thrombophilias is frequently problematic in this age-group, as physiologic levels of protein S and antithrombin are not seen until 6 months of age, and mature levels of protein C may not occur until a child reaches adolescence. Furthermore, coagulant proteins may be artificially low in the setting of acute VTE (see Chapter 527).

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. Usually, 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.

Thrombophilia may be inherited or acquired and may manifest in neonates and in older infants, children, and adolescents. **Inherited thrombophilias** include deficiencies of antithrombin, protein C, and protein S, as well as pathogenic variants of factor V Leiden (FVL) and prothrombin G20210 pathogenic variant (see Chapter 527). The most frequent inherited thrombophilia is the FVL pathogenic variant. It is more common in people of European descent and relatively uncommon in those of African and Asian heritage. Acquired thrombophilic conditions include the presence of lupus anticoagulant (may be present without the diagnosis of systemic lupus erythematosus), anticardiolipin antibody, and anti-β₂-glycoprotein 1 antibody. Methylenetetrahydrofolate reductase (MTHFR) pathogenic variants associated with high levels of plasma homocysteine have also been hypothesized to be a risk factor for VTE, but the prognostic significance is unclear, and an isolated MTHFR pathogenic variant is not an absolute indication for VTE prophylaxis. Diagnostic testing for thrombophilic disorders is unlikely to be beneficial in the acute management of VTE but may be indicated to determine risk of recurrent VTE in both the index case and their relatives. Avoidance of prothrombotic risk factors such as oral contraceptive agents may also be recommended in those individuals with an inherited thrombophilia.

Sickle cell disease is associated with an increased risk for PE and pulmonary infarction. The primary risk factor for VTE in sickle cell disease is the presence of an indwelling CVC. Other risk factors for thrombosis include infection, splenectomy, and immobility.

The incidence of VTE in female adolescents 12–18 years of age is ~3 per 10,000. In patients with known exposure to estrogen-containing long-acting reversible contraception (LARC), more than 96% also had one or more comorbidities. Over 50% of those with VTE had four or more comorbidities. The most common comorbid conditions were obesity and tobacco use. Although estrogen is a known procoagulant, VTE in female adolescents does not appear attributable *solely* to estrogen-containing LARC, and additional risk factors should be sought in affected individuals.

Epidemiology

A wide range of incidence of PE has been described in both hospitalized (8.6–57 per 100,000) children and in the general population (0.14–0.9 per 100,000). There is a suggestion that the incidence of PE has increased over time. The etiology for these increases in pediatric thromboembolism is

Table 458.1 Risk Factors for Pulmonary Embolism

ENVIRONMENTAL	
Long-haul air travel (>4 hr)	
Obesity	
Cigarette smoking	
Hypertension	
Immobility	
WOMEN'S HEALTH	
Oral contraceptives, including progesterone-only and, especially, third-generation pills	
Pregnancy or puerperium	
Hormone replacement therapy	
Septic abortion	
MEDICAL ILLNESS	
Personal or family history of prior pulmonary embolism or deep venous thrombosis	
Cancer	
L-Asparaginase therapy	
Heart failure	
Chronic obstructive pulmonary disease	
Diabetes mellitus	
Inflammatory bowel disease	
Antipsychotic drug use	
Long-term indwelling central venous catheter	
Permanent pacemaker	
Internal cardiac defibrillator	
Stroke with limb paresis	
Spinal cord injury	
Nursing home confinement or current or repeated hospital admission	
SURGICAL	
Trauma, including fractures	
Orthopedic surgery	
General surgery	
Neurosurgery, especially craniotomy for brain tumor	
Vascular anomalies	
May-Turner syndrome	
THROMBOPHILIA	
Factor V Leiden mutation	
Prothrombin gene (20210G A) pathogenic variant	
Hyperhomocysteinemia (including pathogenic variant in methylenetetrahydrofolate reductase)	
Antiphospholipid antibody syndrome	
Deficiency of antithrombin III, protein C, or protein S	
High concentrations of factor VIII or XI	
Increased lipoprotein (a)	
Heparin-induced thrombocytopenia	
Paroxysmal nocturnal hemoglobinuria	
Nephrotic syndrome	
NONTHROMBOTIC	
Air	
Foreign particles (e.g., hair, talc, as a consequence of intravenous drug misuse)	
Amniotic fluid	
Bone fragments, bone marrow	
Fat	
Tumors (Wilms tumor)	

Modified from Goldhaber SZ. Pulmonary embolism. *Lancet*. 2004;363:1295–1305.

regarded as multifactorial, with increased survival from chronic and critical illnesses, increased frequency of indwelling CVCs, increased clinical suspicion, and more precise imaging and diagnostic techniques being cited as contributing factors. The 2-year mortality rate from PE in two studies was ~8.5%, with the highest mortality rates occurring in infants. In other analyses, inpatient VTE has been estimated to increase the risk of mortality by two to six times. Massive PE has historically been associated with death in up to 30% of cases. Currently, the mortality from PE in children approximates the rates of mortality from VTE. In survivors of VTE, chronic complications, increased healthcare use, and increased healthcare costs are recognized.

The incidence of pediatric VTE is recognized as having a bimodal distribution, with peaks occurring in infants less than 1 year of age and in adolescence. Males are statistically more likely to have VTE, except for the 13- to 18-year-old age-group, where females are affected more frequently.

Pediatric deaths from isolated pulmonary emboli are rare. 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 pediatric VTE/PE registry found ~65% 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. VTE is most common in segmental pulmonary arteries (52%), with central arteries being obstructed less frequently (6%). In children, emboli that obstruct <50% of the pulmonary circulation are generally clinically silent unless there is significant coexistent cardiopulmonary disease. When greater than 50% of the pulmonary circulation is obstructed, 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 421). The vascular supply to lung tissue is abundant, and pulmonary infarction is unusual with PE but may result from distal arterial occlusion and alveolar hemorrhage.

CLINICAL MANIFESTATIONS

The presentation of VTE is highly variable and more likely to present atypically or silently in the pediatric age-group. A high index of suspicion is therefore necessary. The symptoms reported most in association with PE include chest pain, hypoxia (cyanosis), dyspnea, tachycardia, tachypnea, and syncope. A tenderness, swelling, or palpable cord may be palpated at the location of a DVT. Hemoptysis may also be a presenting symptom. Pleuritic chest pain is the most common presenting symptom in adolescents (84%). Massive PE may manifest as cardiopulmonary (hypotension) failure. Confirmatory testing should follow a clinical suspicion for PE.

In older adolescents and adults, clinical prediction rules have been published and are based on risk factors, clinical signs, and symptoms (Table 458.2). The Pulmonary Embolism Rule Out Criteria (PERC) and Wells criteria are clinical prediction rules that are commonly used in adults but lack reliability in the pediatric population. The Wells score has a sensitivity of 72–86% and a specificity of 60% when applied to children. The PERC tool has a higher sensitivity but a specificity of only 24% in children. When the PERC tool is applied in the pediatric setting, a high false-positive rate is seen, with over 75% of patients without PE having a positive PERC result. In a population at high risk from exposure to ionizing radiation, more discerning tools have been sought for this age-group.

In children and adolescents less than 22 years of age, the risk of PE is low (1.3%) in children who were not receiving estrogen therapy or in those who did not present with tachycardia or hypoxia ($\text{SpO}_2 < 95\%$); the prediction model reported a sensitivity of 89% and a specificity of 56%. Another clinical prediction model for the diagnosis of PE in adolescents and young adults identified five risk factors, including immobilization, hypercoagulability, exposure to estrogen-containing drugs, indwelling CVC, and a prior history of PE and/or DVT; the probability of PE as demonstrated by computed tomography pulmonary angiography (CTPA) with the presence of any three or more risk factors was 89%, and the probability of PE was extremely low (0.5%) when none of these risk factors were identified. These data and prediction tools may allow risk stratification and optimal use of diagnostic testing, including CTPA, but require prospective analysis and clinical validation.

Table 458.2 Scores to Assess the Clinical Probability of Venous Thromboembolism

WELLS SCORE FOR DEEP VEIN THROMBOSIS		POINTS
Active cancer		+1
Paralysis, paresis, or recent plaster cast on lower extremities		+1
Recent immobilization >3 days or major surgery within past 4 wk		+1
Localized tenderness of deep venous system		+1
Swelling of entire leg		+1
Calf swelling >3 cm compared with asymptomatic side		+1
Unilateral pitting edema		+1
Collateral superficial veins		+1
Previously documented deep vein thrombosis		+1
Alternative diagnosis at least as likely as deep vein thrombosis		-2
<i>Clinical pretest probability</i>		
Unlikely	Total score ≤2 (prevalence 4%)	
Likely	Total score >2 (prevalence 27%)	
WELLS SCORE FOR PULMONARY EMBOLISM		
<i>Original</i>		
Alternative diagnosis less likely than pulmonary embolism		+3
Clinical signs and symptoms of deep vein thrombosis		+3
Heart rate >100 beats per min		+1.5
Previous deep vein thrombosis or pulmonary embolism		+1.5
Immobilization or surgery within the past 4 wk		+1.5
Active cancer		+1
Hemoptysis		+1
<i>Clinical Pretest Probability</i>		
Low	Total score ≤1 (prevalence 4%)	
Intermediate	Total score 2-6 (prevalence 21%)	
High	Total score >6 (prevalence 67%)	
Unlikely	Total score ≤4 (prevalence 8%)	
Likely	Total score >4 (prevalence 41%)	
<i>Simplified</i>		
Alternative diagnosis less likely than pulmonary embolism		+1
Clinical signs and symptoms of deep vein thrombosis		+1
Heart rate >100 beats per min		+1
Previous deep vein thrombosis or pulmonary embolism		+1
Immobilization or surgery within the past 4 wk		+1
Active cancer		+1
Hemoptysis		+1
<i>Clinical Pretest Probability</i>		
Unlikely	Total score ≤1 (prevalence 11%)	
Likely	Total score >1 (prevalence 36%)	
REVISED GENEVA SCORE FOR PULMONARY EMBOLISM		
<i>Original</i>		
Heart rate ≥95 beats per min		+5
Heart rate 75-94 beats per min		+3
Pain on lower-limb deep venous palpation and unilateral edema		+4
Unilateral lower-limb pain		+3

Table 458.2 Scores to Assess the Clinical Probability of Venous Thromboembolism—cont'd

REVISED GENEVA SCORE FOR PULMONARY EMBOLISM	
Previous deep vein thrombosis or pulmonary embolism	+3
Active cancer	+2
Hemoptysis	+2
Surgery or fracture within the past 4 wk	+2
Age >65 yr	+1
<i>Clinical Pretest Probability</i>	
Low	Total score <4 (prevalence 9%)
Intermediate	Total score 4-10 (prevalence 28%)
High	Total score >10 (prevalence 72%)
<i>Simplified</i>	
Heart rate ≥95 beats per min	+2
Heart rate 75-94 beats per min	+1
Pain on lower-limb deep venous palpation and unilateral edema	+1
Unilateral lower-limb pain	+1
Previous deep vein thrombosis or pulmonary embolism	+1
Active cancer	+1
Hemoptysis	+1
Surgery or fracture within the past 4 wk	+1
Age >65 yr	+1
<i>Clinical Pretest Probability</i>	
Unlikely	Total score ≤2 (prevalence 13%)
Likely	Total score >2 (prevalence 42%)
YEARS CRITERIA FOR PULMONARY EMBOLISM	
Clinical signs of deep vein thrombosis	+1
Hemoptysis	+1
Pulmonary embolism is the most likely diagnosis	+1
<i>Clinical Pretest Probability</i>	
Low	Total score 0 (prevalence 3%)
High	Total score ≥1 (prevalence 23%)
PULMONARY EMBOLISM RULE-OUT CRITERIA	
Age <50 yr	—
Heart rate <100 beats per min	—
Pulse oximetry reading on room air >94%	—
No unilateral leg swelling	—
No hemoptysis	—
No recent trauma or surgery	—
No history of venous thromboembolism	—
No oral hormone use	—

Pulmonary embolism can be considered excluded in patients with all Pulmonary Embolism Rule-Out Criteria and a low clinical pretest probability, assessed by gestalt, or in clinical settings with a low (<5%) prevalence of pulmonary embolism. If any criterion applies, pulmonary embolism cannot be ruled out in these patients. Prevalence estimates correspond to emergency department settings. Vital signs should be age adjusted.

Modified from Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. Lancet. 2021;398:64-77.

LABORATORY FINDINGS AND DIAGNOSIS

Blood gas analysis is expected to reveal hypoxemia with an abnormal A-a gradient. Lower-than-normal Paco_2 levels may also be seen secondary to hyperventilation, a finding that may persist even when oxygenation is optimized. Abnormalities of oxygenation and ventilation are likely to be less significant in the pediatric population, in

the setting of less underlying cardiopulmonary disease and greater reserve. The results of an electrocardiogram and chest radiograph are expected to be nonspecific. ECG findings may include ST-T segment changes, tachycardia, right axis deviation, and right bundle branch block. Chest radiographs are frequently abnormal (88%); the most common finding is cardiomegaly (27%) and pleural

effusion (23%). These studies lack sensitivity and specificity in the diagnosis of PE.

A review of results of a complete blood count and coagulation profile is warranted. Prothrombotic diseases should be highly suspected based on medical or family history; additional laboratory evaluations include fibrinogen assays, protein C, protein S, and antithrombin III studies and analysis for FVL pathogenic variant, along with evaluation for lupus anticoagulant and anticardiolipin antibodies.

Echocardiograms may be used to assess ventricular size and function. An echocardiogram is indicated 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; in pediatrics, the utility of ultrasonography is limited, as it may not detect thrombi in the upper extremities or pelvis (Fig. 458.1A).

In children, D-dimer levels demonstrate reasonable sensitivity but poor specificity for venous thrombosis because D-dimer levels are also increased in infectious, inflammatory, and neoplastic disorders, all of which are also risk factors for PE. Other studies have suggested that D-dimer may be a sensitive tool for PE in adolescents when a level of >750 mg/mL is seen; these data have not been found to be applicable to younger children or neonates.

In the evaluation of a suspected PE, a ventilation-perfusion ($\dot{V}-\dot{Q}$) radionuclide scan is a safe diagnostic study associated with exposure to low levels of ionizing radiation. With a definitive or high-probability scan, the likelihood of PE is 85%. With low-probability results, there is still a 20% chance of PE. In addition, children may have difficulty cooperating with the ventilation portion of the $\dot{V}-\dot{Q}$ scan.

Although conventional pulmonary angiography had been considered the gold standard for detection of PE, the invasive nature of this study, the high exposure to radiation, and the risk of complications have limited its use. *Computed tomography/multidetector CT with pulmonary angiography has become the diagnostic study of choice for PE (see Fig. 458.1B)*. The criteria for PE include two or more consecutive images revealing a complete or partial filling defect of a pulmonary artery. 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. Dual-energy scanning provides additional functional and anatomic information without additional radiation exposure. In most institutions, dose reduction techniques can be employed to limit a child's radiation exposure.

Magnetic resonance angiography (MRA) is also considered a viable diagnostic option for patients with VTE. High-resolution 3D contrast-enhanced MRA and time-resolved MRA are sensitive and specific for PE. The lack of ionizing radiation is attractive, but longer imaging times and the need for general anesthesia in most children may limit its use.

TREATMENT

In the acute management of VTE, careful monitoring and support of cardiopulmonary stresses are crucial. Once the affected individual has been stabilized, the primary approach to treatment of VTE is with anticoagulation. Appropriate and timely treatment with anticoagulation may prevent thrombus extension and recurrence. It is also indicated to prevent embolization.

Evaluations for prothrombotic disease must precede anticoagulation. Acute-phase anticoagulation therapy may be provided with unfractionated heparin (UFH) or low molecular weight heparin (LMWH). UFH binds reversibly to antithrombin III and potentiates its ability to inhibit thrombin and coagulation factor Xa. LMWH has become the drug of choice for both short-term and longer-term anticoagulation in children; enoxaparin is the LMWH most used in the pediatric population. It acts similarly to inhibit factor Xa but 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. UFH may still be chosen in 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

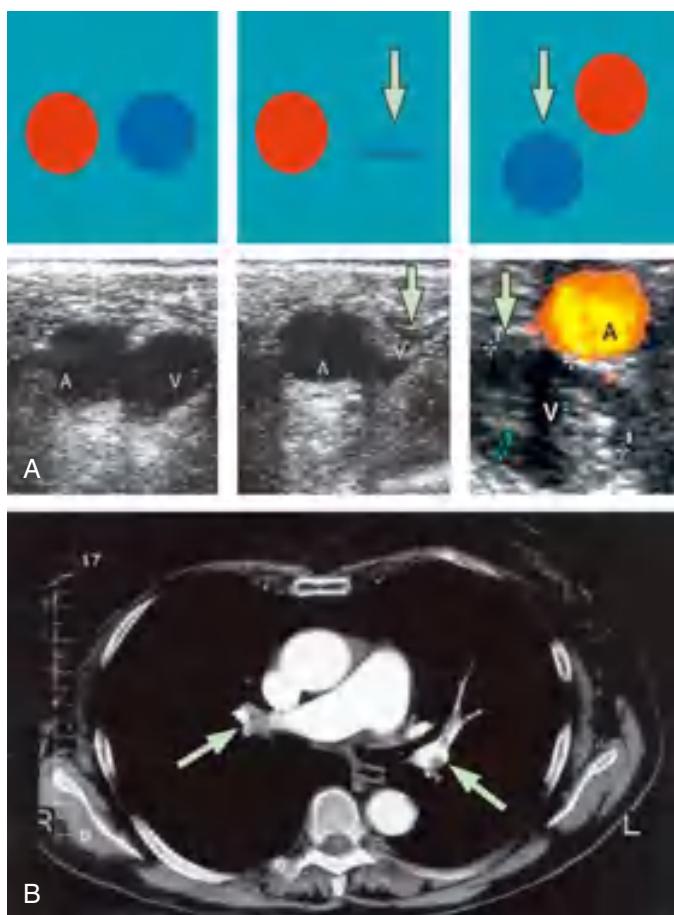


Fig. 458.1 A, Compression ultrasound. Top images, from left to right, representation of vein and artery without and with (arrow) gentle compression with the echocardiographic probe. Bottom images, corresponding echocardiographic findings. The third image from the left shows a thrombus in the vein (vein not compressible by the probe). B, CT angiography showing several emboli (arrows) in the main right pulmonary artery and in left lobar and segmental arteries. A, Artery; V, vein. (From Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379:1835–1844, Fig. 2, p. 1838.)

range is 0.50–1.0 units/mL. When the anti-Xa assay is not available, the activated partial thromboplastin time may be used, with a goal of 60–85 seconds, 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 heparin-induced thrombocytopenia, bleeding, and osteoporosis.

THERAPEUTIC OPTIONS

Extension of anticoagulation therapy occurs in the subacute phase and may use LMWH, LMWH analogues, or warfarin. Warfarin is a vitamin K antagonist that may be used in children and adolescents; use is generally initiated after establishing effective anticoagulation with heparin because severe congenital deficiencies of protein C may be associated with warfarin skin necrosis. When the international normalized ratio (INR) is measured between 1.0 and 1.3, the starting dose for warfarin in children is recommended as 0.2 mg/kg administered orally once daily. Titration of dosing may be needed to achieve a therapeutic INR of 2 to 3. Dosing requirements may vary, and clinical pharmacologic correlation is required. 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 before invasive procedures. The use of an anticoagulation team and/or established treatment algorithms is recommended in order to optimize patient safety.

With the first occurrence of VTE, anticoagulation is recommended for 3–6 months 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 months) and in those with chronic clinical risk factors (12 months to lifelong). In the setting of a congenital thrombophilic condition, the duration of therapy is often indefinite. Inhibitors of factor Xa (e.g., enoxaparin) may become an alternative therapy for both acute PE and long-term treatment (Table 458.3).

In adults with DVT or PE, subsequent therapy with apixaban, dabigatran, edoxaban, or rivaroxaban (direct oral anticoagulants [DOACs]) is recommended over vitamin K antagonists. Some pediatric centers have adapted this therapy, particularly for adolescent patients. The recommended duration of such therapy for uncomplicated patients is 3 months.

Thrombolytic agents such as recombinant tissue plasminogen activator by peripheral vein may be used in combination with anticoagulants in the early stages of treatment; their use is most likely to be considered in children with hemodynamically significant PE (hypotension, echocardiogram evidence of right ventricular dysfunction) or other severe potential clinical sequelae of VTE. Combined therapy may reduce the incidences of progressive thromboembolism, PE, and postthrombotic syndrome. The mortality rate appears to be unaffected by additional therapies; nonetheless, the additional theoretical 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.

Catheter-assisted thrombus removal (thrombectomy) should be limited to those with large emboli that result in persistent hemodynamic compromise refractory to standard therapy. Catheter-assisted

thrombus removal (less often, surgical embolectomy) is indicated in patients with hypotension who are a high bleeding risk or have failed systemic thrombolysis or are in life-threatening shock before systemic thrombolysis can be effective (within hours of thrombolysis). Surgical embolectomy is indicated with embolic Wilms tumor.

In adults with acute proximal DVT of the leg, inferior vena cava filters are used *only* if there is a contraindication to anticoagulation 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 because of the thrombosis or secondary to anticoagulation). Chronic complications include recurrence and pulmonary hypertension with the risk of cor pulmonale. Conditions associated with a poorer prognosis include malignancy, infection, and cardiac disease. The mortality rate in children from PE is 2.2%. An exhaustive evaluation for underlying pathology is advocated in an effort to prevent recurrence and progressive disease. Postthrombotic syndrome is a recognized complication of pediatric thrombotic disease. Venous valvular damage can be initiated by the presence of DVT and may result in persistent venous hypertension with ambulation and valvular reflux. Symptoms include edema, pain, increases in pigmentation, and ulcerations. Affected pediatric patients may suffer lifelong disability.

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Table 458.3 Anticoagulant Therapies for Deep Vein Thrombosis and Pulmonary Embolism

	ROUTE	RENAL CLEARANCE (%)	HALF-LIFE	INITIAL TREATMENT DOSING	MAINTENANCE TREATMENT DOSING	EXTENDED TREATMENT DOSING
Unfractionated heparin (UFH)	Intravenous	~30	~1.5 hr	Maintain aPTT 1.5 times upper limit of normal		
Low molecular weight heparin (LMWH)	Subcutaneous	~80	3-4 hr	Weight-based dosing	Weight-based dosing*	
Fondaparinux	Subcutaneous	100	17-21 hr	Weight-based dosing	Weight-based dosing	
Vitamin K antagonists	Oral	Negligible	Acenocoumarol 8-11 hr; warfarin 36 hr; phenprocoumon 160 hr	Target at INR at 2.0-3.0 and give parallel heparin treatment for at least 5 days	Maintain INR at 2.0-3.0	Maintain INR at 2.0-3.0
Dabigatran	Oral	~80 [†]	14-17 hr	Requires at least 5 days heparin lead-in	150 mg twice a day	150 mg twice a day
Rivaroxaban	Oral	~33 [‡]	7-11 hr	15 mg twice a day for 3 wk	20 mg once a day	20 mg once a day
Apixaban	Oral	~25 [‡]	8-12 hr	10 mg twice a day for 1 wk	5 mg twice a day	2.5 mg twice a day
Edoxaban	Oral	~35 [‡]	6-11 hr	Requires at least 5 days heparin lead-in	60 mg once a day [§]	60 mg once a day [§]
Aspirin	Oral	~10	15 min			80-100 mg once a day

*Treatment with low molecular weight heparin is recommended for patients with active cancer and pregnant women.

[†]Dabigatran is contraindicated in patients with a creatinine clearance below 30 mL/min.

[‡]Apixaban, edoxaban, and rivaroxaban are contraindicated in patients with a creatinine clearance below 15 mL/min.

[§]The recommended edoxaban dose is 30 mg once a day for patients with a creatinine clearance of 30-50 mL/min, a body weight less than or equal to 60 kg, or for those on certain strong P-glycoprotein inhibitors.

Medication dosing may vary with regard to primary diagnosis, age, comorbidities, and other factors. Clinical-pharmacologic correlation is advocated.

aPTT, Activated partial thromboplastin time; INR, international normalized ratio.

From Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet*. 2016;388:3060-3069, Table 2.

458.2 Pulmonary Hemorrhage and Hemoptysis

Mary A. Nevin

Hemoptysis may be defined as the expectoration of blood from the lower respiratory tract. Infants and small children lack the tussive force to expectorate blood, and if blood from the lower airway is expectorated, it is frequently swallowed. Pulmonary hemorrhage in children and adolescents is uncommon but represents a serious and potentially fatal occurrence in children.

Etiology

Table 458.4 and **Table 457.1** in **Chapter 457** present conditions that can manifest as pulmonary hemorrhage or hemoptysis in children. The most common etiologies for pulmonary hemorrhage in the neonate and infant are congenital heart disease, premature lung disease, and coagulopathy (congenital or acquired with liver failure or anticoagulant medications). Infection and foreign body aspiration are the most common etiologies for hemoptysis in children. The chronic presence of a foreign body can lead to localized airway inflammation and hemorrhage. Secondary infection may also be present if the foreign body has been in the airway for days to weeks. Bleeding is more likely to occur in association with a chronically retained foreign body of vegetable origin.

Hemorrhage may be related to chronic airway inflammation and infection with bronchiectasis in the setting of cystic fibrosis (CF). Non-CF bronchiectasis may also be seen in children with chronic aspiration disorders, immunodeficiency syndromes, primary ciliary dyskinesia with

Table 458.4 | Etiology of Pulmonary Hemorrhage (Hemoptysis)

FOCAL HEMORRHAGE

- Bronchitis and bronchiectasis (especially cystic fibrosis related)
- Infection (acute or chronic), pneumonia, abscess
- Tuberculosis
- Trauma
- Pulmonary arteriovenous malformation (with or without hereditary hemorrhagic telangiectasia)
- Foreign body (chronic)
- Neoplasm, including hemangioma and metastatic disease
- Pulmonary embolus with or without infarction
- Bronchogenic cysts

DIFFUSE HEMORRHAGE

- Idiopathic of infancy
- Congenital heart disease (including pulmonary hypertension, venoocclusive disease, and congestive heart failure)
- Prematurity
- Cow's milk hyperreactivity (Heiner syndrome)
- Goodpasture syndrome
- Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis)
- IgA vasculitis (Henoch-Schönlein purpura) and other vasculitic disorders
- Granulomatous disease (granulomatosis with polyangiitis)
- Celiac disease
- Coagulopathy (congenital or acquired)
- Malignancy
- Immunodeficiency
- Exogenous toxins, especially inhaled
- Hyperammonemia
- Pulmonary hypertension
- Pulmonary alveolar proteinosis
- Idiopathic pulmonary hemosiderosis
- Tuberous sclerosis
- Lymphangiomyomatosis or lymphangioleiomyomatosis
- Physical injury or abuse
- Catamenial
- Vaping

See also **Table 457.1**.

or without Kartagener syndrome, HIV, and other infections. Hemoptysis attributable to inflammation and erosion of bronchial and bronchiolar airways may therefore occur in these clinical settings as well. Pulmonary hemorrhage caused by infection is also seen in patients with cavitary disease in association with tuberculosis. Hemoptysis may also occasionally reflect the intense inflammation of an acute pulmonary infection such as bronchitis or bronchopneumonia.

Bleeding is frequently encountered in patients with tracheostomies and is often attributable to suction trauma or friable granulation tissue. In these situations, bleeding tends to be limited and responsive to modifications of the care regimen. Rarely, bleeding from a tracheostomy may be brisk and bright red. In this case, otolaryngology should evaluate for the presence of a tracheo-innominate artery fistula.

Cardiopulmonary disease is associated with hemoptysis in children and adolescents. Associated conditions include mitral stenosis, pulmonary edema in the setting of congestive heart failure, high-altitude pulmonary edema (HAPE), pulmonary venous obstructive disease, and pulmonary hypertension. Although early corrective surgical intervention has been associated with improved hemodynamics, collateral circulations may contribute to bleeding.

Traumatic injury to the airway and pulmonary contusion may result from motor vehicle crashes or other direct-force injuries. 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 17**). Factitious hemoptysis may rarely be encountered in the setting of self-inflicted trauma to the oral mucosa by biting or in the setting of factitious disorder by proxy (formerly Munchausen by proxy; see **Chapter 17.2**).

Rare causes for hemoptysis include tumors and vascular anomalies such as arteriovenous malformations (AVMs) (**Fig. 458.2**). Congenital vascular malformations in the lung may be seen in the setting of **hereditary hemorrhagic telangiectasia (HHT)**. Symptoms and signs of pulmonary AVM include dyspnea, hemoptysis, poor exercise tolerance, digital clubbing, and cyanosis. A high index of suspicion is needed, as more than half of children with pulmonary AVM may be asymptomatic. AVMs in individuals with HHT may be associated with severe complications, including massive hemoptysis, hemothorax, and stroke. In individuals with HHT, pulmonary AVMs are prevalent (60%) and can occur at any age. Any tumors or lesions must be cautiously investigated when encountered with a flexible fiberoptic bronchoscope, as bleeding may be massive and difficult to control.

Bronchial **Dieulafoy disease** has been recognized as a rare etiology for pulmonary hemorrhage. The classic bronchoscopic appearance is a small, submucosal bronchial lesion with a white cap. Massive hemorrhage may ensue. If nonsurgical bronchial artery embolization is not able to achieve hemostasis, surgical resection of the affected lung segment or lobe may be considered.

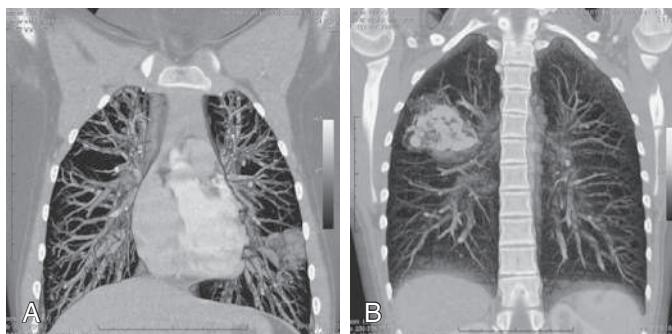


Fig. 458.2 A, Volume-rendering reconstruction of the contrast-enhanced spiral CT showing a large arteriovenous fistula in the left upper lobe (lingula). B, Volume-rendering reconstruction of the contrast-enhanced spiral CT showing an arteriovenous fistula in the right upper lobe. (From Grzela K, Krenke K, Kulus M. Pulmonary arteriovenous malformations: clinical and radiological presentation. *J Pediatr*. 2011;158:856, Figs. 1 and 2.)

Syndromes associated with vasculitic, autoimmune, and idiopathic disorders may be associated with diffuse alveolar hemorrhage (see Chapter 457).

EPIDEMIOLOGY

The frequency with which pulmonary hemorrhage occurs in the pediatric population is difficult to define. The difficulties in timely diagnosis are primarily related to the variability in disease presentation. As such, the incidence of pulmonary hemorrhage may be significantly underestimated. Chronic bronchiectasis as seen in CF (see Chapter 454) or ciliary dyskinesia (see Chapter 455) can cause hemoptysis, but usually occurs in children older than 10 years of age.

PATOPHYSIOLOGY

The vascular supply of the lung has two components. The pulmonary artery provides blood to the bronchi to the level of the terminal bronchioles and to the alveolar capillary bed. The pulmonary circulation is characterized by low pressure and high volume. Conversely, the bronchial circulation originates from the aorta or intercostal arteries. The pressure in the bronchial artery circulation is systemic. This circulation provides blood to the conducting airways. Hemoptysis may occur from either the pulmonary or bronchial circulation. Bleeding from the pulmonary circulation is expected to be insidious; slow bleeding in the lower airways typically manifests with anemia, fatigue, and dyspnea, and hemoptysis may be absent. Syndromes associated with diffuse alveolar hemorrhage are discussed in Chapter 457. Bleeding from the bronchial circulation may be massive and associated with rapid exsanguination. Blood that comes from the lung is frequently difficult to differentiate from blood that originates at the nasopharynx, mouth, or gastrointestinal (GI) tract. The blood that originates from the airway is classically bright red or rust colored. Alveolar blood may have a frothy appearance. Blood originating from the GI tract is typically brownish in color. The pH of pulmonary blood is alkaline, whereas blood from the GI tract is expected to be acidic.

In patients with CF, chronic endobronchial infection, inflammation, mucus plugging, and thickening of the airway surface layer predispose to growth and dilation of the bronchial arteries. Blood in the airway is highly irritative and initiates an influx of neutrophils and inflammatory mediators that serve to exacerbate the already vibrant inflammatory response. As such, pulmonary hemorrhage may be recurrent in late-stage CF. Massive and life-threatening hemorrhage may occur. With repeated or chronic hemorrhage, pulmonary fibrosis can become a prominent pathologic finding.

CLINICAL MANIFESTATIONS

The presenting symptoms and signs of pulmonary hemorrhage are highly variable in the pediatric population. Older children and young adults experiencing focal hemorrhage may be able to localize the bleeding by a sensation of “warmth” or “bubbling” in the chest. This can occasionally aid the clinician in locating the area involved. Rapid and large-volume blood loss manifests as hypoxicemic and hypercarbic respiratory failure and hypovolemic shock. Chronic, insidious blood loss may manifest as anemia, fatigue, dyspnea, or poor exercise tolerance. Severely anemic individuals may present with syncope. Radiographic infiltrates may be seen in a focal or diffuse distribution on chest radiograph. The presence of a cavitary lesion or radiopaque foreign body suggests tubercular or fungal infection and foreign body aspiration, respectively.

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 in acute blood loss. The diagnosis of pulmonary hemorrhage is best confirmed by bronchoscopy with direct visualization of bleeding and/or a bronchoalveolar lavage specimen that confirms the presence of **hemosiderin-laden macrophages** on Prussian blue staining. Within 48-72 hours of an episode of bleeding, alveolar macrophages convert the iron from erythrocytes into hemosiderin. It may take weeks to clear these hemosiderin-laden macrophages

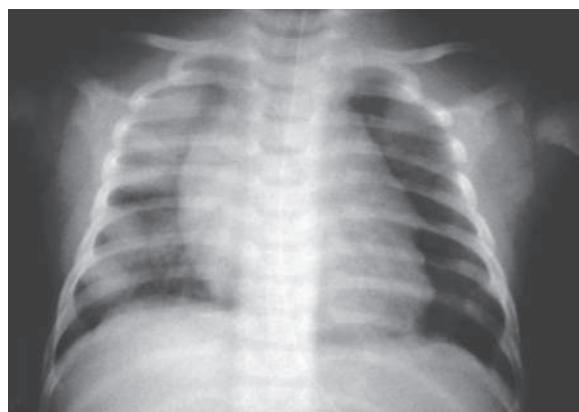


Fig. 458.3 Radiographic appearance of acute idiopathic pulmonary hemorrhage in infancy. (From Brown CM, Redd SC, Damon SA, Centers for Disease Control and Prevention. Acute idiopathic pulmonary hemorrhage among infants: recommendations from the Working Group for Investigation and Surveillance. MMWR Recomm Rep. 2004;53:1-12.)

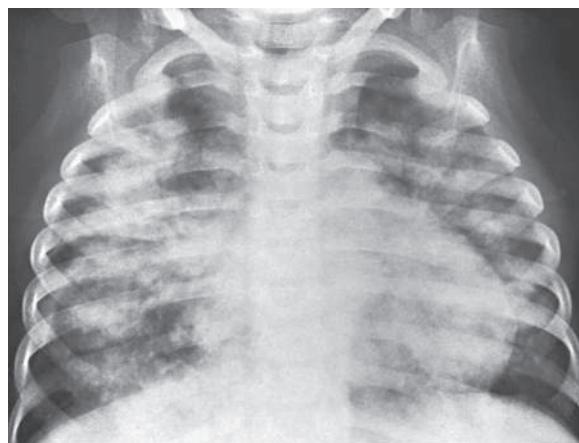


Fig. 458.4 Diffuse pulmonary hemorrhage that was thought to be the result of idiopathic pulmonary hemosiderosis in a 3-yr-old child. Frontal radiograph reveals bilateral air space consolidation that is patchy. Tracheal washing contained large numbers of macrophages filled with hemosiderin. Ten days later, most of the consolidative changes in the lungs had cleared. The patient's anemia was successfully treated with blood transfusion. (Courtesy Bertram Girdany, MD, Pittsburgh, PA; from Slovis T, ed. Caffey's Pediatric Diagnostic Imaging, 11th ed. Philadelphia: Mosby; 2008.)

completely from the alveolar spaces, thereby allowing differentiation between acute and chronic hemorrhage.

Chest radiographs may demonstrate fluffy bilateral densities, as seen in acute idiopathic pulmonary hemorrhage of infancy (Fig. 458.3) or the patchy consolidation seen in idiopathic pulmonary hemosiderosis (Fig. 458.4). 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 intraalveolar hemoglobin for carbon monoxide.

TREATMENT

In mild to moderate hemoptysis (>5 mL blood), potential irritants to the lung (hypertonic saline, DNase, chest physiotherapy, and inhaled antibiotics) are typically held. In patients with CF, vitamin K may be given empirically, given a predilection toward vitamin K deficiency with comorbid pancreatic insufficiency.

In the setting of massive hemorrhage (>240 mL), emergent circulatory and ventilatory support is provided and a requirement for volume resuscitation and transfusion of blood products should be anticipated. If respiratory failure ensues, mechanical ventilatory support with high positive end-expiratory pressure (PEEP) may tamponade a bleeding vessel and improve oxygenation. If bleeding is unilateral, selective ventilation of the unaffected lung may be recommended. Rigid bronchoscopy may be used for localization of bleeding and for removal of debris, but active bleeding may be exacerbated by airway manipulation. In patients with CF who are unstable with massive hemorrhage, proceeding directly to bronchial artery embolization (BAE) has been advocated. Improved outcomes of BAE have been seen when the bleeding vessel is identified by multidetector CT imaging. Cessation of bleeding is achieved in approximately 80% of patients, but bleeding may be recurrent, and more than one BAE may be required. Rare complications include inadvertent embolization of spinal and mesenteric arteries, leading to paralysis and ischemic bowel, respectively. If embolization fails, total or partial lobectomy may be required.

Antifibrinolytic therapy with tranexamic acid (TXA) has been used to control bleeding in patients with hemophilia and in patients with CF, as well as in other conditions (bronchiectasis, tuberculosis, allergic bronchopulmonary aspergillosis). This medication may be administered by inhaled, oral, or parenteral routes. Inhaled TXA may be as effective as intravenous dosing; the inhaled route has fewer systemic effects. The use of this medication is currently off label.

Depending on institutional capabilities, extracorporeal membrane oxygenation (ECMO) and emergent listing for lung transplantation may also be considered for patients with end-stage disease.

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Chapter 459

Atelectasis

Ranna A. Rozenfeld

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 five groups (Table 459.1). Respiratory syncytial virus (see Chapter 307) 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 one or both lungs is most often a postoperative complication but occasionally results from other causes, such as trauma, asthma, pneumonia, tension pneumothorax (see Chapter 461), aspiration of foreign material (see Chapters 435 and 446), 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.

Table 459.1 Anatomic Causes of Atelectasis

CAUSE	CLINICAL EXAMPLES
External compression on the pulmonary parenchyma	Pleural effusion, pneumothorax, intrathoracic tumors, diaphragmatic hernia
Endobronchial obstruction completely obstructing the ingress of air	Enlarged lymph node, tumor, cardiac enlargement, foreign body, mucoid plug, broncholithiasis
Intraluminal obstruction of a bronchus	Foreign body, asthma, granulomatous tissue, tumor, secretions including mucous plugs, bronchiectasis, pulmonary abscess, chronic bronchitis, acute laryngotracheobronchitis, plastic bronchitis
Intrabronchiolar obstruction	Bronchiolitis, interstitial pneumonitis, asthma
Respiratory compromise or paralysis	Neuromuscular abnormalities, osseous deformities, overly restrictive casts and surgical dressings, defective movement of the diaphragm, or restriction of respiratory effort

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 respiration, 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.

Massive atelectasis usually presents with dyspnea, cyanosis, and tachycardia. An affected child is extremely anxious and, if old enough, complains of chest pain. The chest appears flat on the affected side, where decreased respiratory excursion, dullness to percussion, and feeble or absent breath sounds are also noted. Postoperative atelectasis usually manifests within 24 hours of operation but may not occur for several days.

Acute lobar collapse is a frequent occurrence in patients receiving intensive care. If undetected, it can lead to impaired gas exchange, secondary infection, and subsequent pulmonary fibrosis. Initially, hypoxemia may result from ventilation-perfusion mismatch. In contrast to atelectasis in adult patients, in whom the lower lobes and, in particular, the left lower lobe is most often involved, 90% of cases in children involve the upper lobes and 63% involve the right upper lobe. There is also a high incidence of upper lobe atelectasis and, especially, right upper lobe collapse in patients with atelectasis being treated in neonatal intensive care units. This high incidence may be a result of the movement of the endotracheal tube into the right mainstem bronchus, where it obstructs or causes inflammation of the bronchus to the right upper lobe.

DIAGNOSIS

The diagnosis of atelectasis can usually be established by chest radiograph. Typical findings include volume loss and displacement of fissures. Atypical presentations include atelectasis manifesting as a masslike opacity and atelectasis in an unusual location. Lobar atelectasis may be associated with pneumothorax. Several studies have shown

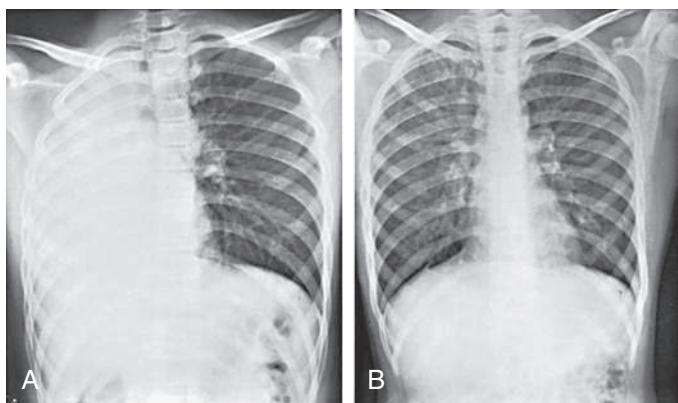


Fig. 459.1 A, Massive atelectasis of the right lung. The patient has asthma. The heart and other mediastinal structures shift to the right during the atelectatic phase. B, Comparison study after reaeration subsequent to bronchoscopic removal of a mucous plug from the right mainstem bronchus.

lung ultrasound to be a viable alternative to chest radiograph when diagnosing atelectasis, especially in patients with neuromuscular disease, to avoid radiation exposure.

In children with asthma, 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 426.1). Atelectasis is more common when diagnosis of foreign-body aspiration is delayed for greater than 2 weeks. 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 atelectasis is typically 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. 459.1).

TREATMENT

Treatment depends on the cause of the collapse (Table 459.2). 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 the nebulized

Table 459.2 Treatment for Atelectasis	
CAUSE OF ATELECTASIS	TREATMENT
Pleural effusion or pneumothorax	Relieve compression
Mucus plug	Tracheal or bronchoscopic aspiration Continuous positive airway pressure
Foreign body	Bronchoscopic examination
Asthma	Bronchodilator and corticosteroid treatment Recombinant human deoxyribonuclease (off-label use) Hypertonic saline with or without bronchodilator
Neuromuscular diseases	Intermittent positive pressure breathing Mechanical insufflator-exsufflator Noninvasive bilevel positive pressure ventilation
Cystic fibrosis	Airway clearance therapies Hypertonic saline with or without bronchodilator Recombinant human deoxyribonuclease

form for nonintubated patients with acute asthma and intratracheally for atelectasis in intubated asthmatics, with resolution of atelectasis unresponsive to conventional asthma therapies. Recombinant human deoxyribonuclease is also used 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 used in the outpatient and inpatient setting and in both the neonatal intensive care unit and the pediatric intensive care unit to help facilitate airway clearance, though studies of its use in bronchiolitis have had mixed results (see Chapter 439.1). Lobar atelectasis in cystic fibrosis is discussed in Chapter 454.

Atelectasis can occur in patients with neuromuscular diseases. These patients tend to have an 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 reintubation. In ventilated patients, positive-end expiratory pressure or continuous positive airway pressure is generally indicated.

Airway clearance therapies used for adults are often recommended and/or used 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. Thus far, no specific airway clearance therapy has been demonstrated to be superior.

Chapter 460

Pulmonary Tumors

John Palla and Susanna A. McColley

See also Chapter 438.

Primary tumors of the lung are rare in children and adolescents (Table 460.1). 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 malignant tumors; bronchial carcinoid tumors represent ~80%. Pediatric carcinoid tumors are predominantly low-grade malignancies, but children with these tumors should be evaluated and monitored by a pediatric oncologist. Carcinoid syndrome from a bronchial carcinoid tumor is rare in children. Metastatic lesions are the most common forms of pulmonary malignancy in children; primary processes include Wilms tumor, osteogenic sarcoma, germ cell tumors, and hepatoblastoma (see Part XX, 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 a primary cystic lesion or is associated with a congenital pulmonary airway malformation (see Chapter 444.3). Lymphoma is the most common cause of mediastinal mass in children; other mediastinal tumors include thymoma, thyroid cancer, and teratoma. Neuroblastoma may present as a posterior mediastinal mass.

Table 460.1 Pulmonary Tumors in Children

MALIGNANT

Bronchial adenomas (40–60%)
Carcinoid
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Pleuropulmonary blastoma (15%)
Bronchogenic carcinoma (10–15%)
Adenocarcinoma
Small-cell carcinoma
Bronchoalveolar carcinoma
Squamous-cell carcinoma
Undifferentiated carcinoma
Fetal-lung adenocarcinoma
Pulmonary mesothelioma
Sarcomas (20–25%)
Rhabdomyosarcoma
Synovial sarcoma
Hemangiopericytoma (solitary fibrous tumor)
Leiomyosarcoma
Angiosarcoma
Bronchopulmonary fibrosarcoma

BENIGN

Hamartomas
Hemangiomas
Lymphangioma
Leiomyomas
Myofibroblastic tumors
Inflammatory myofibroblastic tumor
Myofibromatosis
Congenital peribronchial myofibroblastic tumor
Neurogenic tumors
Mature teratoma

From Goldberg JM, Pappo AS, Bishop M. Rare tumors of childhood. In Orkin SH, Fisher DE, Ginsburg D, et al., eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*, 8th ed. Philadelphia: Elsevier; 2015: Table 65.4, p. 2130.

CLINICAL MANIFESTATIONS AND EVALUATION

There is often a delay in the diagnosis of pediatric pulmonary tumors given their rarity and nonspecific presenting symptoms. Pulmonary tumors may manifest as fever, hemoptysis, wheezing, cough, pleural effusion, chest pain, dyspnea, recurrent or persistent pneumonia, and/or atelectasis. Localized wheezing, and wheezing unresponsive to bronchodilators, can occur with bronchial tumors. Tumors may be suspected from plain chest radiographs; however, CT or MRI imaging of the chest is necessary for precise anatomic definition (Table 460.2; Figs. 460.1 and 460.2). Depending on the

Table 460.2 Imaging Characteristics of Primary Malignant Lung Tumors

NEOPLASM	IMAGING CHARACTERISTICS
Inflammatory myofibroblastic tumor (IMT)	Solitary (95%) or multiple (5%) Usually sharply circumscribed, lobulated mass Typically located in the peripheral portion of the lungs Soft tissue mass with either homogeneous or heterogeneous attenuation may have both solid and cystic and calcific components
Carcinoid or salivary gland tumor	Centrally located lesion: intraluminal soft tissue mass with distal atelectasis or obstructive pneumonitis Peripherally located lesion: oval or lobulated intraluminal or exophytic mass and occasionally calcify
Bronchogenic carcinoma	Central mass lesion with bronchial obstruction or, less commonly, small peripheral lesion
Pleuropulmonary blastoma	Cystic or mixed cystic and solid lesion adjacent to pleura; can be very large, with mediastinal displacement
Epithelioid hemangioendothelioma	Multiple well- or ill-defined nodular opacities up to 3 cm in diameter; very rare in childhood

From Chu WCW, Epelman M, Lee EY. Neoplasia. In Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: Table 55.3, p. 531.

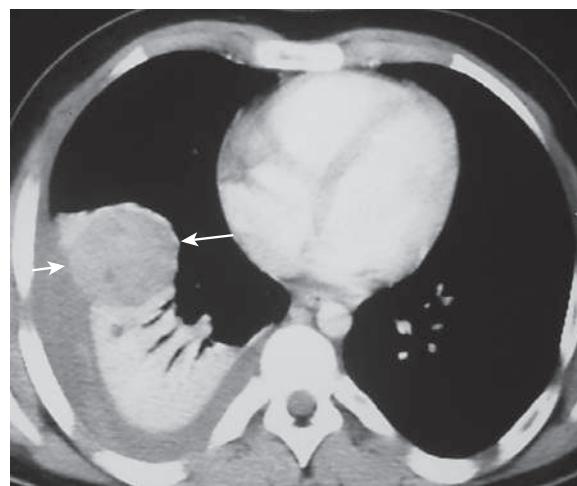


Fig. 460.1 Inflammatory myofibroblastic tumor. An afebrile 13-yr-old male who presented with increasing dyspnea and right-sided pleuritic chest pain. Axial contrast-enhanced CT of the chest shows a rounded heterogeneously enhancing lesion (arrows) located adjacent to an area of atelectatic lung. Pleural fluid at the same level demonstrates increased attenuation consistent with a hemithorax. (Modified from Chu WCW, Epelman M, Lee EY. Neoplasia. In Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: Fig. 55.8A, p. 531.)



Fig. 460.2 Adenoid cystic carcinoma. A 14-yr-old male with a progressively worsening chronic cough and respiratory difficulty for 1 yr who presented with hoarseness and crepitus over the neck. **A**, Chest radiograph shows pneumomediastinum (arrowheads) and an apparent soft tissue density projecting over the carina (arrows). **B**, Coronal contrast-enhanced CT image shows a lobulated soft tissue mass (arrows) centered near the carina, which results in the narrowing of the adjacent airway. **C**, Axial contrast-enhanced T1-weighted MRI demonstrates avid enhancement of the mass (arrows). (From Chu WCW, Epelman M, Lee EY. Neoplasia. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019. Fig. 55.11: p. 532.)

tumor size and location, pulmonary function tests may be normal or may show an obstructive, restrictive, or mixed pattern; there is no responsiveness to bronchodilators. Bronchial tumors are occasionally diagnosed during fiberoptic bronchoscopy performed for persistent or recurrent pulmonary infiltrates or hemoptysis (see Chapter 438).

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.

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young adults, most frequently in males who are tall and thin and thought to have subpleural blebs. Smoking cigarettes, marijuana, crack cocaine, e-cigarette vaping, and ecstasy/MDMA (methylene-dioxymethamphetamine) have been associated with developing a pneumothorax.

A pneumothorax arising as a complication of an underlying lung disorder but without trauma is a **secondary spontaneous pneumothorax**. Familial cases of spontaneous pneumothorax occur and have been associated with pathogenic variants in the folliculin gene (*FCLN*). Over 150 unique *FCLN* variants have been associated with the **Birt-Hogg-Dube syndrome** (skin fibrofolliculomas, multiple basal lung cysts, renal malignancies) or in patients with familial or recurrent spontaneous pneumothoraces. Individuals with other inherited disorders, such as α_1 -antitrypsin (see Chapter 442) and homocystinuria, are also predisposed to pneumothorax. Patients with collagen synthesis defects such as vascular Ehlers-Danlos syndrome (see Chapter 700) and Marfan syndrome (see Chapter 743) are at increased risk for the development of pneumothorax.

Pneumothorax can occur in pneumonia, usually with empyema; it can also be secondary to a 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 can be found in children hospitalized with asthma exacerbations and usually resolves without treatment. Pneumothorax is a serious complication of cystic fibrosis (see Chapter 454). Pneumothorax also occurs in patients with lymphoma or other malignancies and in graft-versus-host disease with bronchiolitis obliterans. Catamenial pneumothorax, an unusual condition that is related to menses, is associated with diaphragmatic defects and pleural blebs.

External chest or abdominal blunt or penetrating trauma can tear a bronchus or abdominal viscera, with leakage of air into the pleural space. 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.

Pneumothorax can be associated with a serous effusion (hydropneumothorax), a purulent effusion (pyopneumothorax), or blood (hemopneumothorax). Bilateral pneumothorax is rare after the neonatal period but has been reported after lung transplantation and with *Mycoplasma pneumoniae* infection and tuberculosis.

Chapter 461

Pneumothorax

Suraiya K. Haider and Aarthi P. Vemana

Pneumothorax is the accumulation of extrapulmonary air within the chest, most commonly from leakage of air from within the lung. Air leaks can occur spontaneously and be classified as primary or secondary, or occur due to trauma or an iatrogenic cause (Table 461.1). Pneumothorax in the neonatal period is also discussed in Chapter 132.

Etiology and Epidemiology

A **primary spontaneous pneumothorax** occurs without trauma or obvious underlying lung disease. Spontaneous pneumothorax with or without exertion occurs occasionally in teenagers and

Table 461.1 Causes of Pneumothorax in Children**SPONTANEOUS****Primary Idiopathic (no underlying lung disease)**

Spontaneous rupture of subpleural blebs
Drug use (smoking cigarettes, marijuana, crack cocaine, use of e-cigarettes)
Valsalva maneuver

Secondary (underlying lung disease)**Congenital lung disease**

- Congenital pulmonary airway malformation
- Bronchogenic cysts
- Pulmonary hypoplasia
- Birt-Hogg-Dube syndrome

Conditions associated with increased intrathoracic pressure

- Asthma
- Bronchiolitis
- Cystic fibrosis
- Airway foreign body

Infection

- Tuberculosis
- *Pneumocystis jirovecii*
- Echinococcosis
- Pneumatocele
- Lung abscess
- Bronchopleural fistula
- COVID-19 infection

Lung disease

- Langerhans cell histiocytosis
- Tuberous sclerosis
- Marfan syndrome
- Vascular Ehlers-Danlos syndrome
- Pulmonary fibrosis
- Sarcoidosis
- Rheumatoid arthritis, scleroderma, ankylosing spondylitis
- Metastatic neoplasm—usually osteosarcoma (rare)
- Pulmonary blastoma
- Catamenial

TRAUMATIC**Noniatrogenic**

Penetrating trauma

Blunt trauma

Iatrogenic

Thoracotomy

Thoracoscopy, thoracentesis

Tracheostomy

Tube or needle puncture

Mechanical ventilation

High-flow therapy (moved from noniatrogenic)

CLINICAL MANIFESTATIONS

The onset of pneumothorax is usually abrupt, and the severity of symptoms depends on the extent of the lung collapse and the amount of preexisting lung disease. Pneumothorax may cause dyspnea, chest 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 retractions; 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 bronchial breath sounds 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. 461.1–461.6). The amount of air outside the lung varies with time. A radiograph that is taken early shows less lung collapse than one that was taken later if the leak continues. Expiratory views accentuate the contrast between lung markings and the clear area of the pneumothorax (see Fig. 461.1). Variations exist in the measurement techniques defining the size of a pneumothorax. A large pneumothorax is measured by The American College of Chest Physicians as ≥3 cm from the lung apex to the thoracic cupola, and by the British Thoracic Society as ≥2 cm from the lung margin to the chest wall at the level of the hilum (Table 461.2).

It may be difficult to determine whether a pneumothorax is under tension. Tension pneumothorax is present when there is a 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. On occasion, the diagnosis of tension pneumothorax is made only based on evidence of circulatory compromise or on hearing a "hiss" of rapid exit of air under tension with the insertion of the thoracostomy tube. 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. 461.3).

Pneumothorax must be differentiated from localized or generalized emphysema, an extensive emphysematous bleb, large pulmonary cavities or other cystic formations, diaphragmatic hernia, compensatory overexpansion with contralateral atelectasis, and gaseous distention of the stomach. In most cases, chest radiography or CT differentiates among these possibilities. In addition, CT may identify underlying pathology such as blebs (Fig. 461.7). Further evaluation to determine if a diaphragmatic hernia is present should include a barium swallow with a small amount of barium to demonstrate that it is not free air but is a portion of the gastrointestinal tract that is in the thoracic cavity (see Chapter 131). Ultrasound can also be used to establish the diagnosis.

TREATMENT

Therapy varies with the extent of the collapse and the nature and severity of the underlying disease. A small or even moderate-sized pneumothorax in an otherwise normal child may resolve without specific treatment, usually within 1 week. 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 the administration of supplemental oxygen. Pleural pain deserves analgesic treatment.

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 **tension pneumothorax**, a 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 causing hemodynamic instability.

Adapted from Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. *Eur Respir Rev*. 2010;19(117):217–219, 2010. Tables 1 & 2, p. 218.

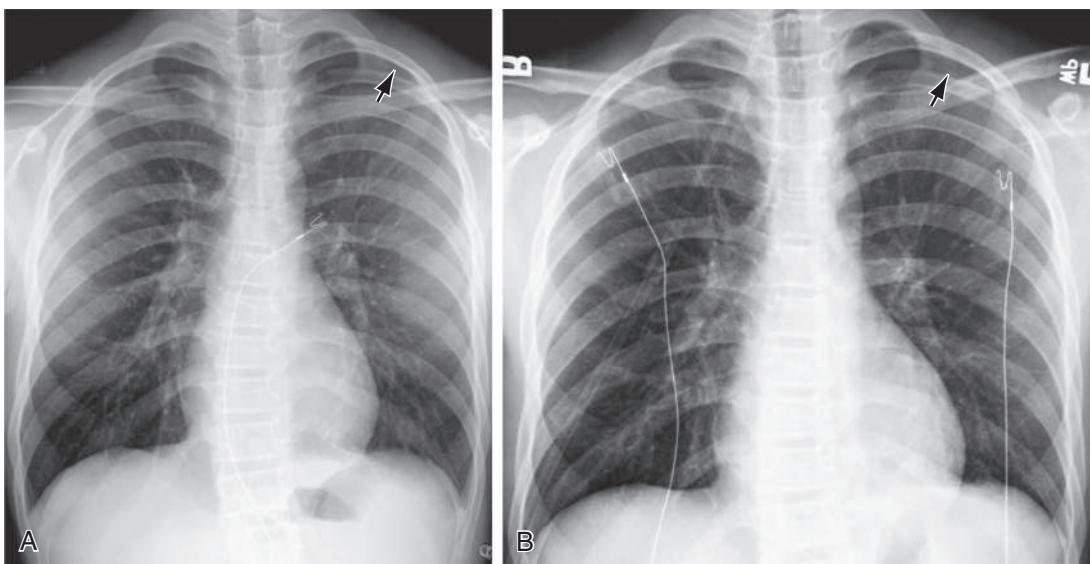


Fig. 461.1 Utility of an expiratory film in detection of a small pneumothorax. A, Teenager with stab wound and subtle radiolucency in the left apical region (arrow) on inspiratory chest radiograph. The margin of the visceral pleura is very faintly visible. B, On an expiratory film, the pneumothorax (arrow) is more obvious as the right lung has deflated and become more opaque, providing better contrast with the air in the pleural space.

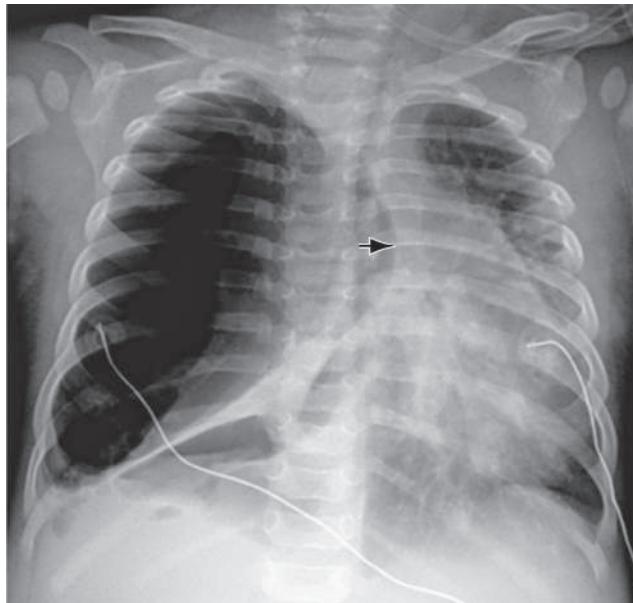


Fig. 461.2 Right pneumothorax, with lung collapse of a compliant lung. Shift of the mediastinum to the left (arrow) indicates that this is a tension pneumothorax.

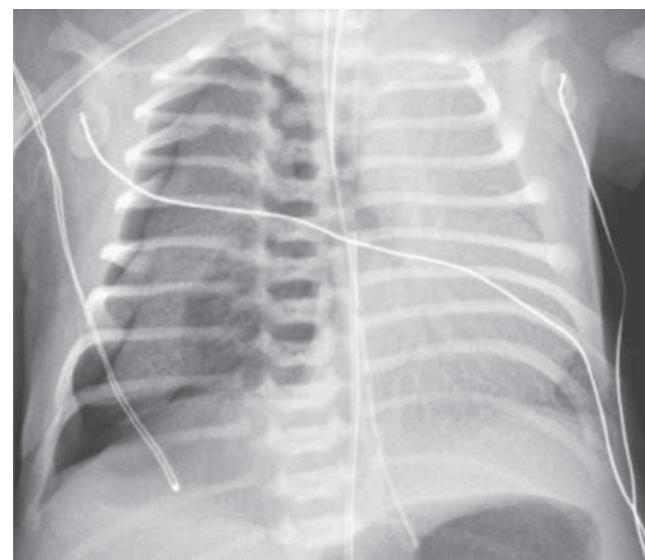


Fig. 461.3 Right pneumothorax, with only limited collapse of a poorly compliant lung.

Needle aspiration into the second intercostal space in the midclavicular line 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 more than a small collapse, catheter drainage or other invasive measures may be necessary. Pneumothorax in patients with cystic fibrosis or Marfan syndrome 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 leaks 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. Consideration can be given to a sclerosing procedure to induce the formation of

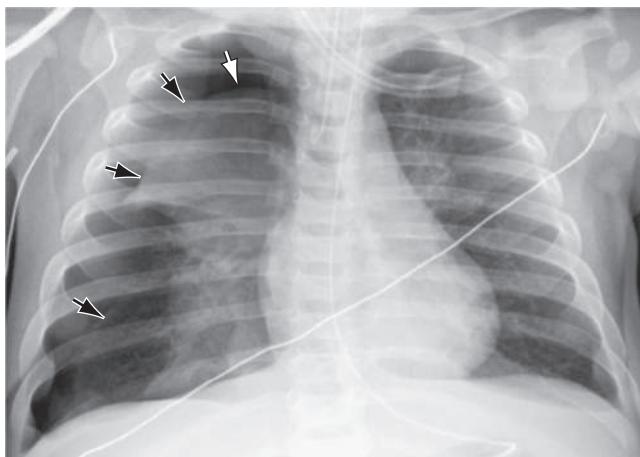


Fig. 461.4 Pneumothorax, with collapse of right lung (arrows), caused by barotrauma in a 7-mo-old child who was intubated for respiratory failure.

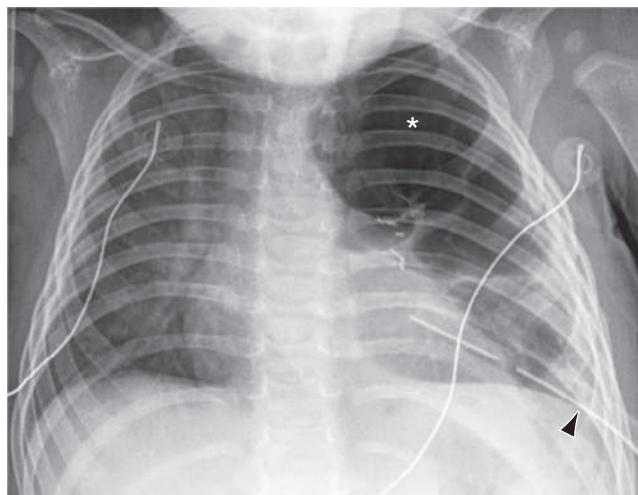


Fig. 461.6 Bronchopleural fistula following surgical resection of the left upper lobe as a result of congenital lobar emphysema. Chest radiograph shows localized pneumothorax (asterisk) that persisted despite prior insertion of a large-bore chest tube (arrowhead).

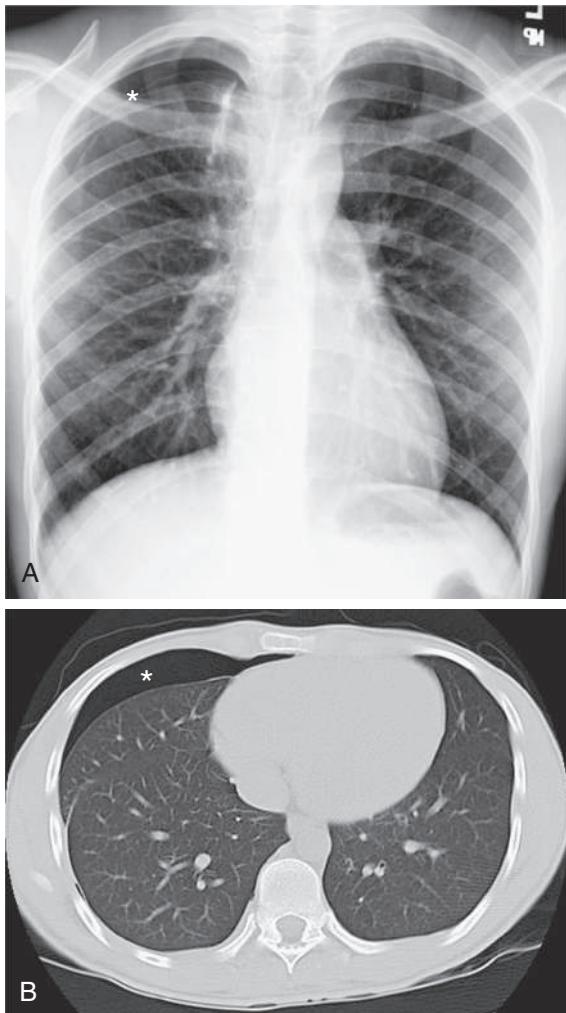


Fig. 461.5 Teenager in whom a spontaneous right pneumothorax developed because of a bleb. Patient had a persistent air leak despite recent surgical resection of the causative apical bleb. Chest radiograph (A) and CT scan (B) clearly show the persistent pneumothorax (asterisk).

strong adhesions between the lung and chest wall with the introduction of doxycycline or iodopovidone into the pleural space (chemical pleurodesis).

Open thoracotomy through a limited incision, with plication of blebs, closure of the 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 *recurrent* pneumothorax. Stripping and abrading the pleura leaves raw, inflamed surfaces that heal with sealing adhesions. Video-assisted thoracoscopic surgery (VATS) is a preferred therapy for blebectomy, pleural stripping, pleural brushing, and instillation of sclerosing agents, with less morbidity than occurs with traditional open thoracotomy. In cases with a persistent air leak following thoracic surgery, an autologous blood patch pleurodesis may also be considered.

There is a risk of recurrence after surgical treatment in the pediatric population, although this is often not related to surgical failure but rather associated with the formation of new or undetected bullae. Clear benefit for treatment of asymptomatic blebs/bullae in the contralateral lung has not been established in the pediatric population.

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), steps should be taken to avoid, if at all possible, chemical or mechanical pleurodesis. 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.

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Table 461.2 Summary of the Main Features of the BTS, Belgian, and ACCP Guidelines for Spontaneous Pneumothorax Management			
	BTS	BELGIAN	ACCP
Definition of large pneumothorax	>2 cm between lung margin and chest wall (at level of the hilum)	≥20% using light index and/or complete dehiscence from lateral chest wall	≥3 cm apex-to-cupola distance
First line small PSP management	Observation if asymptomatic; aspiration if symptomatic	Observation if asymptomatic; aspiration if symptomatic	Observation for 3–6 hr and outpatient follow-up Aspirate or ICC if pneumothorax enlarges Presence of symptoms >24 hr does not alter treatment
First line large PSP management	Observation if asymptomatic; aspiration if symptomatic	Aspiration	Insertion of ICC
First line small SSP management	Admission and insertion of ICC; aspiration can be considered as an alternative	Admission and observation; aspiration if symptomatic	Admission and observation; insertion of ICC if symptomatic
First line large SSP management	Admission and insertion of ICC	Admission and insertion of ICC	Admission and insertion of ICC

BTS, British Thoracic Society; ACCP, American College of Chest Physicians; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax; ICC, intercostal chest catheter.

From Lieu N, Ngo P, Chennapragada SM, et al. Update in management of paediatric primary spontaneous pneumothorax. *Pediatr Respir Rev*. 2022;41:73–79. Table 1.

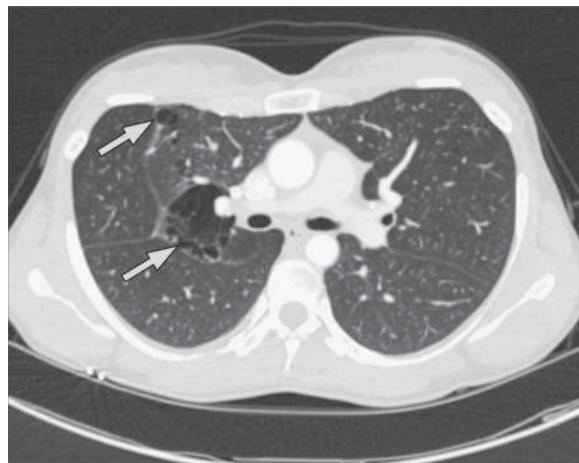


Fig. 461.7 High-resolution CT thorax showing multiple basal cysts. (From Hopkins TG, Maher ER, Reid E, et al. Recurrent pneumothorax. *Lancet*. 2011;377:1624. Fig. 1.)

menses, and diabetes mellitus with ketoacidosis. Traumatic causes of pneumomediastinum include both iatrogenic (dental extractions, adenotonsillectomy, high flow nasal cannula therapy, esophageal perforation, inhalation of helium gas, and flexible bronchoscopy) and noniatrogenic (inhaled foreign body and penetrating chest trauma).

PATHOGENESIS

According to the **Macklin effect**, after an intrapulmonary alveolar rupture, air dissects along the pressure gradient 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. Other symptoms may be present and may include globus pharyngeus, abdominal pain, cough, chest tightness, facial swelling, choking, tachypnea, fever, stridor, and sore throat. Pneumomediastinum is difficult to detect by physical examination alone. Subcutaneous emphysema is present in the majority of patients. When present, **Hamman sign** (a mediastinal “crunch”) is nearly pathognomonic for pneumomediastinum. Cardiac dullness to percussion may be decreased, but if the chest is chronically overinflated, it is unlikely that the clinician can be sure of this finding.

LABORATORY FINDINGS

Chest radiography reveals mediastinal air, with a more distinct cardiac border than normal (Figs. 462.1 and 462.2). A “spinnaker sail sign” or “angel wing sign” occurs when air deviates the thymus upward and outward, which is seen more often in pediatric patients. On the lateral projection, the posterior mediastinal structures are clearly defined, there may be a lucent ring (“ring sign”) around the right pulmonary artery, and retrosternal air can usually be seen. Vertical streaks of air in the mediastinum and subcutaneous air are often observed (see Fig. 462.1). If a pneumomediastinum is clinically suspected but is not visualized on a chest x-ray, a chest CT can be performed to confirm the diagnosis and identify tracheal injury, if present.

TREATMENT

Treatment is directed primarily at the underlying obstructive pulmonary disease or other precipitating condition. Children who have had pneumomediastinum should be screened for asthma. Analgesics are occasionally needed for chest pain. Children can be observed in the emergency room and discharged if stable. They should be cautioned to avoid heavy lifting and the Valsalva maneuver. Hospital admission with supplemental oxygen administration is more common for patients with secondary pneumomediastinum. In severe cases, consideration should be given to

Chapter 462

Pneumomediastinum

Aarthi P. Vemana and Suraiya K. Haider

Air or gas in the mediastinum is called *pneumomediastinum* and is typically caused by alveolar rupture, which can be due to either a spontaneous or traumatic cause. A spontaneous pneumomediastinum can either be primary without an underlying etiology or can occur secondary to an underlying cause. Primary pneumomediastinum can be due to increases in intrathoracic pressure as is seen with a Valsalva maneuver, vomiting, Boerhaave syndrome (esophageal perforation), weightlifting, inhalation of recreational drugs, use of e-cigarettes, recreational use of MDMA, and choking events. Causes of secondary pneumomediastinum include lower respiratory tract infections including COVID-19, asthma exacerbations, mechanical ventilation, anorexia nervosa, normal

the use of more invasive interventions, including tracheotomy, surgical repair, and skin incisions over the neck and anterior chest wall. The use of prophylactic antibiotics to prevent deep neck space infections and mediastinitis has not been shown to provide additional benefit.

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 132 and 461).

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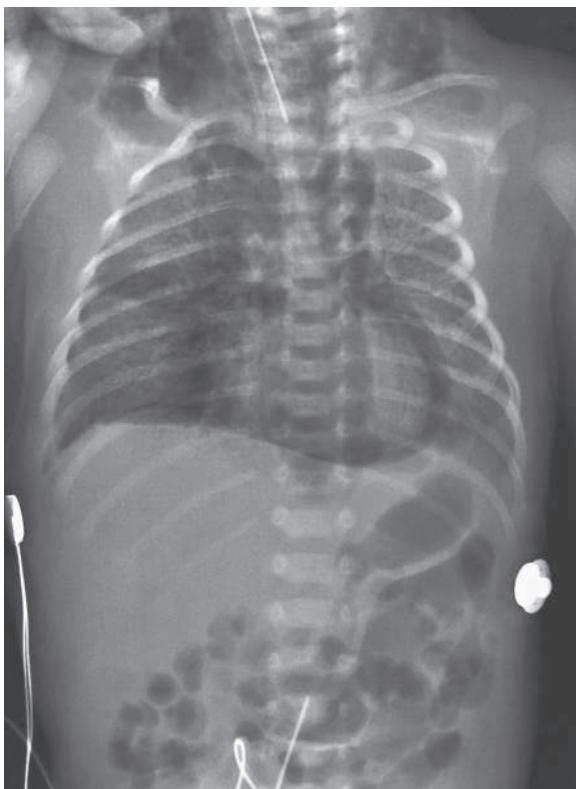


Fig. 462.1 Large pneumomediastinum surrounding the heart and dissecting into the neck. (From Clark DA. *Atlas of Neonatology*, 7th ed. Philadelphia: WB Saunders; 2000.)

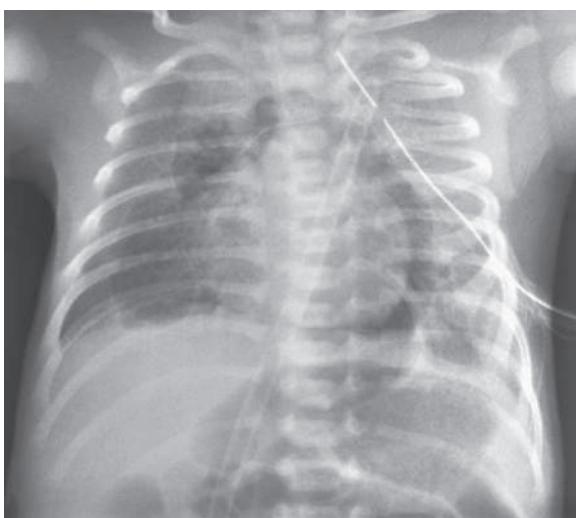


Fig. 462.2 Sail sign—thymic elevation. (From Clark DA. *Atlas of Neonatology*, 7th ed. Philadelphia: WB Saunders; 2000: p. 94.)

Chapter 463

Hydrothorax

Aarthi P. Vemana and Suraiya K. Haider

Hydrothorax is a transudative pleural effusion; typically, it is caused by abnormal pressure gradients in the lung. 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 superior vena cava obstruction by neoplasms, enlarged lymph nodes, pulmonary embolism, or adhesions. It may occur from a ventriculoperitoneal (VP) shunt, central venous catheter, peritoneal dialysis, or after corrective spinal fusion for treatment of adolescent idiopathic scoliosis.

CLINICAL MANIFESTATIONS

Hydrothorax is usually bilateral, but in cardiac or hepatic 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 451.2), but in hydrothorax there is more rapid shifting of the level of dullness with changes of position. Depending on the etiology, it can be associated with an accumulation of fluid in other parts of the body.

LABORATORY FINDINGS

The fluid is **transudative**, noninflammatory, has few cells, and has a lower specific gravity (<1.015) than that of a serofibrinous exudate (see Chapters 449 and 451). 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. In a patient with a VP shunt, B-transferrin assays and radionuclide tracer shunt series may be helpful for diagnosis. Peritoneal scintigraphy may be considered to evaluate for a peritoneal-pleural leak. In hepatic hydrothorax, the pleural fluid resembles spontaneous bacterial peritonitis, with positive bacterial cultures and polymorphonuclear leukocyte counts >250 cell/mm 3 .

TREATMENT

Therapy is directed at the underlying disorder. If a transudative fluid is clinically suspected, aspiration may not be needed unless pressure symptoms are noted or there are atypical symptoms, such as fever, pleuritic pain, or asymmetric effusions. Aspirated fluid may be diagnostic using PCR for bacteria and cytology and flow cytometry for malignancies.

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Chapter 464

Hemothorax

Suraiya K. Haider and Aarthi P. Vemana

Hemothorax, an accumulation of blood in the pleural cavity, is rare in children. 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. 458.2 in Chapter 458), or occur in association with vascular Ehlers-Danlos syndrome. It is also an occasional manifestation of intrathoracic neoplasms, costal exostoses, blood dyscrasias, bleeding diatheses, thrombolytic therapy, thoracic endometriosis, or rarely COVID-19 infections. Rupture of an aneurysm is unlikely during childhood. Hemothorax may occur spontaneously but is rare in 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 451.2), hemothorax is associated with hemodynamic compromise related to the amount and rapidity of bleeding, with ventilatory collapse. Spontaneous hemothorax presents with sudden onset of chest or back pain or dyspnea and can progress rapidly to hemorrhagic shock.

DIAGNOSIS

The diagnosis of a hemothorax is initially suspected from radiographs, ultrasounds, or CT scans but can be made definitively with thoracentesis (Fig. 464.1). In every case, an effort must be made to determine and treat the cause.

TREATMENT

Therapy includes supplemental oxygen, fluid resuscitation (including possible blood transfusion), and tube thoracostomy. Video-assisted thorascopic surgery (VATS) can be considered in most patients with stable vital signs to visualize the source of bleeding, remove blood clots, resect bullae or blebs, and to perform pleurodesis. An open thoracotomy may be indicated if there is uncontrolled bleeding or in a hemodynamically compromised patient. Inadequate removal of blood in extensive hemothorax leading to a retained hemothorax can increase the risk for development of pneumonia, empyema, or substantial restrictive disease secondary to organization of fibrin. Fibrinolytic therapy or a decortication may then be necessary. Embolization is the treatment of choice for an arteriovenous malformation.

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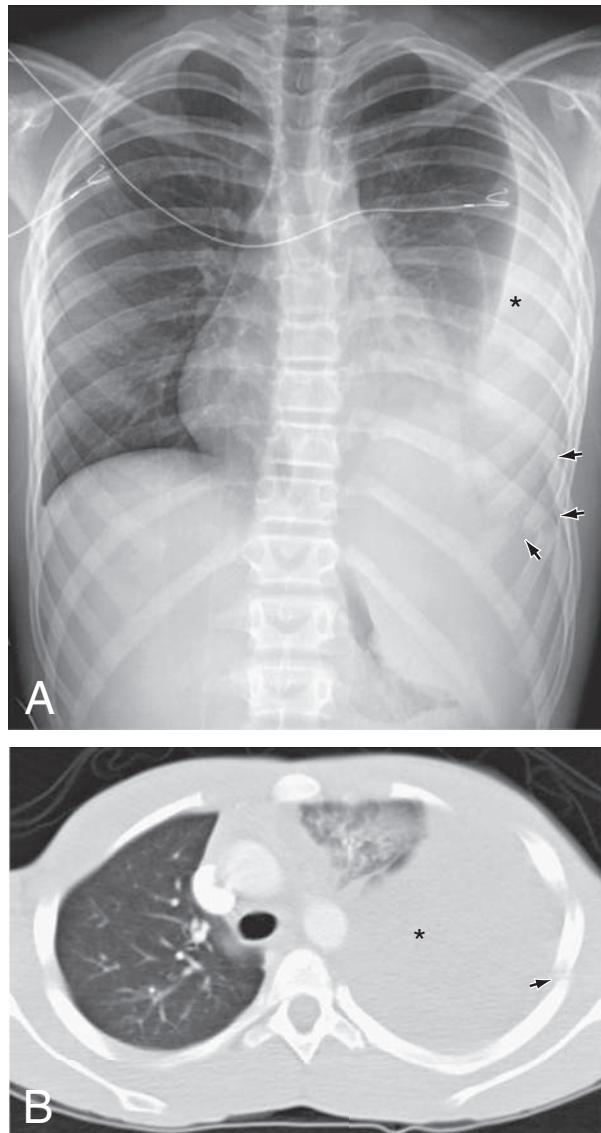


Fig. 464.1 Chest radiograph (A) and CT scan (B) of hemothorax (asterisk) and associated rib fractures (arrows) in a teenager involved in a motor vehicle accident.

Chapter 465

Chylothorax

Suraiya K. Haider and Aarthi P. Vemana

Chylothorax is a pleural collection of fluid formed by the escape of chyle from the thoracic duct or lymphatics into the thoracic cavity. Chylothorax in children occurs most frequently because of thoracic duct injury as a complication of cardiothoracic surgery (post Fontan surgery) (Fig. 465.1). Other cases are associated with chest injury (Fig. 465.2), extracorporeal membrane oxygenation, or primary or metastatic intrathoracic malignancy, particularly lymphoma. In newborns, rapidly increased venous pressure during delivery may lead to thoracic duct rupture. Chylothorax has also been associated with Down syndrome, Noonan syndrome, Turner syndrome, and congenital myotonic dystrophy. Genetic pathogenic variants involving the VEGFC/VEGFR3, PI3K/AKT/mTOR, and RAS/MAPK pathways can impact lymphangiogenesis leading to lymphatic malformations. Refractory chylothorax in the fetus has been associated with a missense variant in integrin $\alpha_9\beta_1$ gene. Persistent or recurrent chylothorax has been described in association with pathogenic variants in the *PIEZO1* gene. Less common causes include lymphangiomatosis (Fig. 465.3), restrictive pulmonary diseases, thrombosis of the duct, superior vena cava, or subclavian vein; tuberculosis or histoplasmosis, Gorham-Stout disease, and congenital anomalies of the lymphatic system (Fig. 465.4). Chylothorax can occur in trauma and child abuse (see Chapter 16). 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, including cough, chest discomfort, and dyspnea. 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 first day of life. Chylothorax is rarely bilateral and usually occurs on the right side.

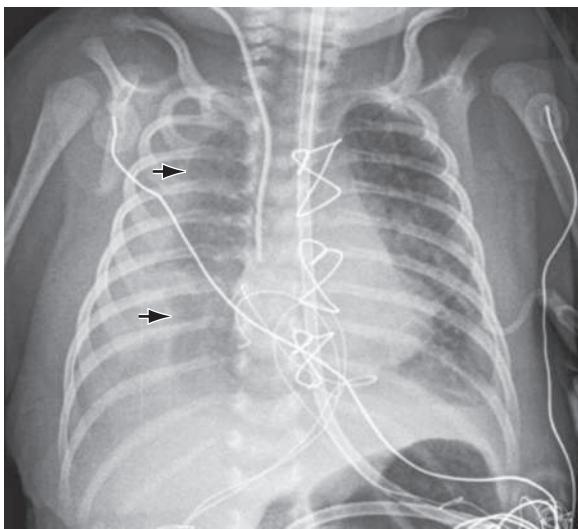


Fig. 465.1 Chylothorax (arrows) following cardiac surgery in a 2-wk-old infant.



Fig. 465.3 Large right chylous effusion opacifying much of the right thorax in a teenager with pulmonary lymphangiomatosis and hemangiomatosis. Note the associated interstitial lung disease.

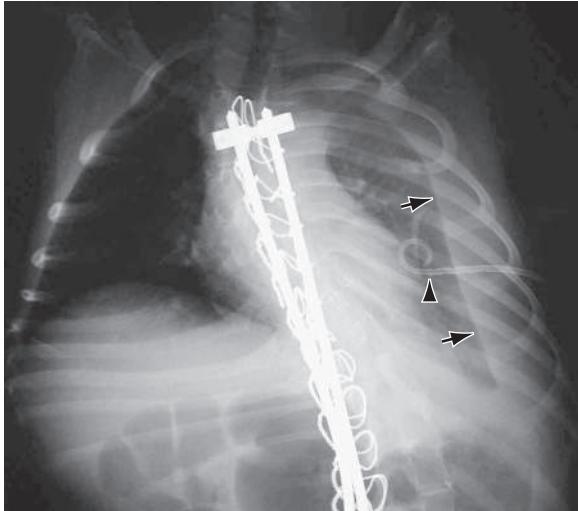


Fig. 465.2 Left chylothorax (arrows) following spinal fusion with Harrington rods. It is postulated that the thoracic duct was injured during spine surgery. The pigtail chest tube (arrowhead) needed to be retracted to better drain the effusion.

LABORATORY FINDINGS AND IMAGING

Chest radiographs can help to delineate the location of an effusion; CT scans show normal pleural thickness and may demonstrate a mediastinal mass such as a lymphoma, as the etiology of the chylothorax. Thoracentesis demonstrates a chylous effusion, a milky fluid containing triglycerides, 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 ($>80\%$) lymphocytes and often exceed 1,000 cells per mm³. After diagnosing chylothorax, a lymphangiogram can localize the site of the leak, and lymphoscintigraphy may

demonstrate abnormalities of the lymphatic trunks and peripheral lymphatics. MR lymphangiography also allows for visualization of the peripheral and segments of the central lymphatics. Dynamic contrast-enhanced magnetic resonance lymphangiography can provide real-time evaluation of the central lymphatic flow with good spatial resolution to guide management options.

TREATMENT

Treatment involves symptomatic support and decreasing or stopping chyle accumulation. Management is divided into two categories: nonsurgical and surgical. Nutritional management strategies include a combination of nil-per-os (NPO) and total parenteral nutrition, or enteral feeds using either a low-fat or medium-chain triglyceride diet or defatted human milk (also known as skimmed human milk). Thoracentesis is repeated as needed to relieve pressure symptoms; tube thoracostomy is often performed. Somatostatin and octreotide have been used to manage chylothorax. Various octreotide dosages have been described, including 1–4 µg/kg/hr intravenously and 10 µg/kg/day subcutaneously. Retrospective analyses have shown beneficial effects with the use of steroids, in particular, hydrocortisone, methylprednisolone, and dexamethasone combined with somatostatin or octreotide. Use of propranolol or sirolimus in severe or refractory cases may be effective. Further studies are required to confirm the optimal dosage for steroids, propranolol, and sirolimus. Other therapeutic approaches include pressure control ventilation with positive end-expiratory pressure and inhalation of nitric oxide. If medical management is unsuccessful, surgical options should be considered and can include a pleuroperitoneal shunt, thoracic duct ligation, and pleurodesis with the use of sclerosing agents such as fibrin glue or povidone-iodine. 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. Etilerfrine, a sympathomimetic agent with both α - and β -adrenergic activity, has been successfully used in a few patients. Constriction of the thoracic duct by this drug may reduce pleural chyle accumulation. Percutaneous thoracic duct embolization or treatment of other lymphatic vessels is a successful interventional radiology strategy. 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.

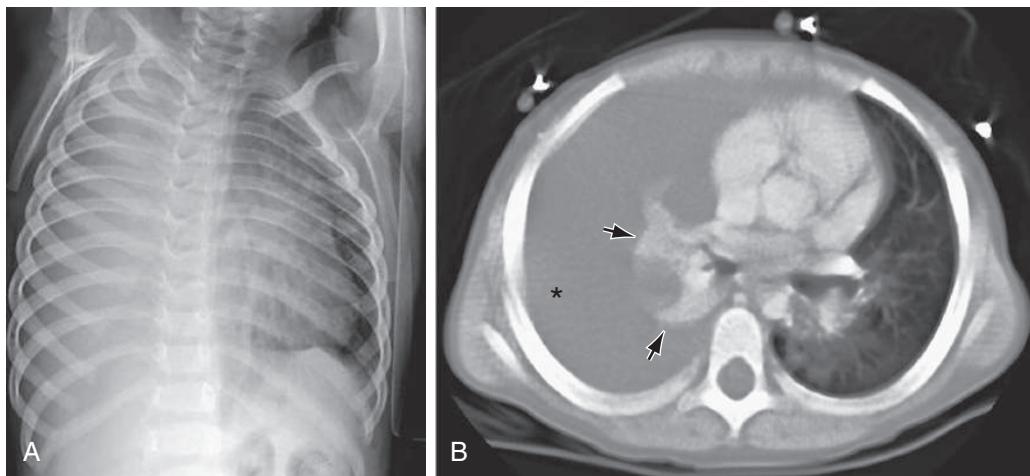


Fig. 465.4 Spontaneous chylothorax in a 4 yr old with a duplication of chromosome 6. A, Chest radiograph shows opacification of the right thorax. B, CT scan shows the chylous pleural effusion (asterisk) compressing the atelectatic lung (arrows).

COMPLICATIONS

If repeated thoracenteses are required due to the rapid reaccumulation of chyle, malnutrition may occur 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 malnutrition, infection, and death.

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CLINICAL MANIFESTATIONS

Physical findings of the pulmonary exam vary with the severity of the disease and with respiratory illnesses. Although some patients may appear to be comfortably breathing when well, they can experience significant deterioration when ill or with periods of stress due to decreased pulmonary reserve secondary to alveolar hypoplasia and small airway disease. Children with BPD may exhibit tachypnea, head bobbing, and retractions when ill or at baseline depending on the severity of the disease. Although breath sounds may be clear, many patients have baseline wheeze or coarse crackles. A persistent, fixed wheeze or stridor suggests subglottic stenosis (see Chapter 436) or large airway malacia. Fine crackles may be present in patients prone to fluid overload. Chest radiographs may demonstrate air trapping, focal atelectasis, interstitial changes, and/or peribronchial thickening.

The most severely affected patients may require respiratory support to achieve adequate gas exchange. Supplemental oxygen may be required to maintain acceptable oxygen saturations and often is needed to minimize the work of breathing. Chronic respiratory insufficiency may be evidenced as elevation of serum bicarbonate, elevated carbon dioxide on blood gas analysis, hypoxemia, or polycythemia; the most severe cases may require tracheostomy and ventilation to achieve long-term respiratory stability. Patients must be monitored for the development of pulmonary hypertension, especially if they require supplemental oxygen and have chronic respiratory insufficiency.

Aspiration from dysphagia and/or gastroesophageal reflux (GERD) (see Chapter 369) can compromise pulmonary status. The risk of aspiration may increase during periods of illness due to worsening tachypnea and air trapping. Other comorbidities resulting from premature birth that complicate the management of BPD include fixed and functional upper airway obstruction, CNS injuries leading to abnormal control of breathing, abnormal airway tone, increased aspiration risk, gastrointestinal dysmotility, systemic hypertension, and poor growth. Of note, infants with significant lung disease can exhibit growth failure from the elevated energy expenditure essential to maintaining the increased metabolic demands of respiration and/or ongoing hypoxia.

A *pulmonary exacerbation* in a child with BPD is typically triggered during viral respiratory infections. Other frequent risk factors for pulmonary exacerbations may include weather changes, exposure to cigarette smoke, exposure to emissions from vaping devices, attending daycare, and aspiration. During an exacerbation, the infant may exhibit increased work of breathing, crackles, and wheezing, with tachypnea and retractions becoming more prominent. Underlying pulmonary hypertension may worsen with pulmonary exacerbations as well.

Chapter 466

Bronchopulmonary Dysplasia

Sharon A. McGrath-Morrow and J. Michael Collaco

Bronchopulmonary dysplasia (BPD) is a chronic lung disease of infancy and childhood that occurs primarily in preterm infants born at less than 32 weeks' gestation. BPD is characterized by alveolar hypoplasia, often with concomitant small airway dysfunction and impaired pulmonary vascular growth. Contributing factors to the development of BPD may include early gestational age, low birthweight, lung barotrauma, exposure to hyperoxia, lung inflammation, and pre- and postnatal infections, as well as potential modifier genes and epigenetic factors. The currently accepted definition for diagnosis includes an oxygen requirement for 28 days postnatally, and the disorder is graded as mild, moderate, or severe based on supplemental oxygen and ventilation requirements at specific time points (Table 466.1). For initial inpatient presentation and management, see Chapter 127.

Table 466.1 Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria

GESTATIONAL AGE	<32 WEEKS	≥32 WEEKS
Time point of assessment	36 weeks' PMA or discharge to home, whichever comes first	>28 days but <56 days' postnatal age or discharge to home, whichever comes first
TREATMENT WITH >21% OXYGEN FOR AT LEAST 28 DAYS PLUS		
Mild BPD	Breathing room air by 36 weeks' PMA or discharge, whichever comes first	Breathing room air by 56 days' postnatal age or discharge, whichever comes first
Moderate BPD	Need for <30% oxygen at 36 weeks' PMA or discharge, whichever comes first	Need for <30% oxygen at 56 days' postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks' PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days' postnatal age or discharge, whichever comes first

BPD, Bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; PMA, postmenstrual age; PPV, positive pressure ventilation.

Adapted from Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163:1723.

TREATMENT

Treatment is directed toward decreasing the work of breathing and normalizing gas exchange to allow for optimal growth and neurodevelopment. After initial hospital discharge, infants and children with BPD are at high risk for rehospitalization. Up to 50% of infants with BPD are readmitted for acute respiratory illnesses within the first 2 years of life. These children also may require multiple daily medications, supplemental oxygen, and/or chronic ventilation.

Adherence to prescribed daily medication regimens may decrease the risk of acute care use and chronic respiratory symptoms; however, there are no standard guidelines for the management of BPD concerning post-NICU care. Although commonly used, there are limited data regarding the efficacy of diuretics in the outpatient setting.

With regard to respiratory support, targeted oxygen saturations should be ≥92% outside of the NICU to ensure adequate growth and neurocognitive development. Pulse-oximetry and polysomnography may be helpful for titration purposes. Before initial hospital discharge, infants and children who require chronic ventilatory support have been shown to benefit from standardized protocols to determine medical readiness, assess familial proficiency in respiratory care, and establish adequate support in an outpatient setting. After discharge, these patients will require close follow-up from pulmonologists and otolaryngologists to manage ventilator titration and weaning and tracheostomy care and decannulation, respectively. As infants and children with tracheostomies are at high risk for adverse events, including death, an awake and alert trained caregiver is recommended at all times.

Pulmonary function testing in children with a history of BPD has consistently demonstrated obstructive small airway disease. Small airway disease in this population may be partially responsive to bronchodilators but may also have a fixed obstructive component. Inhaled corticosteroids and β-agonists may be effective in treating symptoms, such as wheezing or chronic cough.

Adequate caloric intake is important to ensure catch-up lung growth. Some children may require fortified breast milk or formula to achieve adequate growth. Patients at risk for aspiration and those with inadequate oral intake may require tube feeding to meet nutritional goals. Placement of a gastrostomy tube should be considered before discharging home. Aspiration secondary to dysphagia and/or gastroesophageal reflux should be considered in patients with recurrent respiratory symptoms or pneumonia without obvious infectious etiologies. Because of their tenuous respiratory status, some infants and children with BPD may not be able to tolerate even minimal amounts of aspiration from gastroesophageal reflux. There are limited data regarding risks and benefits of antireflux medications in infants with BPD, such as histamine-2 blockers, proton pump inhibitors, and motility agents. Medications that reduce gastric acidity may increase the risk of pneumonia in some children. Consideration for either Nissen fundoplication or gastrojejunostomy tubes may be required in cases of failure of antireflux medical therapy.

Up to 15–25% of infants with severe BPD will be diagnosed with pulmonary hypertension, which may be secondary to decreased pulmonary vascular growth and/or a reactive vascular bed. Other risk factors for developing pulmonary hypertension may include extreme prematurity and decreased intrauterine growth; recurrent aspiration, hypoxia, and hypercarbia may worsen severity. Pulmonary hypertension in infants is associated with increased morbidity and mortality compared to infants without pulmonary hypertension. Although definitive diagnosis of pulmonary hypertension requires cardiac catheterization, in practice transthoracic echocardiography provides a low-risk screening tool. Screening should also attempt to identify potential structural causes of pulmonary hypertension, such as pulmonary vein stenosis. Serum biomarkers, such as brain natriuretic protein, may be useful in tracking response to therapy. Abrupt worsening of pulmonary hypertension (*pulmonary hypertensive crises*) can occur in the context of illnesses and with anesthesia. Crises can occur even in stable children with a history of pulmonary hypertension who become acutely ill. Although pulmonary hypertension that is associated with BPD can improve with adequate lung growth, therapies such as sildenafil and other antipulmonary hypertensive agents have been used in management.

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 307) immunoprophylaxis should be considered based on the severity of lung disease and the patient's gestational age and current age. Another environmental factor that can worsen respiratory symptoms is exposure to secondhand tobacco smoke (see Chapter 759.1).

PROGNOSIS

The prognosis for infants with BPD is generally good, although the presence of BPD may result in a longer initial hospitalization compared with preterm infants without BPD. Most infants are weaned off of oxygen during the first year of life, and those requiring home mechanical ventilation are often weaned from this support during toddlerhood. Many children exhibit an asthma-like phenotype during early childhood, characterized by episodes of wheezing or coughing triggered by upper respiratory tract infections, exertion, allergens, etc. For some of these children, symptoms improve by school age; others may continue to have asthma-like exacerbations with viral illnesses and exercise throughout childhood that may persist into adulthood. Even asymptomatic patients with a history of BPD can continue to demonstrate small airway flow limitations by spirometry. Lastly, obstructive sleep apnea may also be more common in infants, children, and young adults with a history of BPD.

Chapter 467

Skeletal Diseases Influencing Pulmonary Function

Steven R. Boas and Catherine Kier

Pulmonary function is influenced by the structure of the chest wall (see Chapter 421). 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 clefts*, *Poland syndrome*, and skeletal and *cartilage dysplasias*. Vertebral anomalies such as kyphoscoliosis can alter pulmonary function in children and adolescents.

467.1 Pectus Excavatum (Funnel Chest)

Steven R. Boas and Catherine Kier

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 743) or Ehlers-Danlos syndrome (see Chapter 700). 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 ~30% 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. 467.1). Patients may 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 sternal depression. 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 have been used historically to help determine the extent of the anatomic abnormality. However, the correlation of the Haller index with the physiologic compromise or associated systems appears suboptimal. The use of 3D chest optical imaging or “surface scan” is gaining popularity in the evaluation. An electrocardiogram may show a right-axis deviation or Wolff-Parkinson-White syndrome (see Chapter 485); an echocardiogram may demonstrate mitral valve prolapse (see Chapter 477.3) 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. Pulmonary limitations, such as ventilatory limitations and associated flow volume loop abnormalities, are commonly seen in younger children and adolescents, whereas additional 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, the use of physical therapy to address musculoskeletal compromise, corrective surgery, cosmetic surgery, and noninvasive thoroscopic techniques. For patients with significant physiologic compromise, surgical correction may improve the cosmetic deformity and may help minimize progression or even improve the cardiopulmonary compromise. The two main surgical interventions are the Ravitch and Nuss procedures. The Nuss procedure is a minimally invasive thoracoscopic repair that has been associated with good cosmetic and functional outcomes.

The extent of the anatomic defect, including the degree of asymmetry, may help determine the appropriate surgical approach. Although surgical repair may result in improved exercise tolerance for some individuals, usually observed at submaximal exercise intensities, many patients do not show improvement in either respiratory or cardiac function. Normalization of lung perfusion scans and maximal voluntary ventilation have also been observed after surgery. Use of a magnetic brace with gradual remodeling (Magnetic Mini Mover procedure) of the pectus deformity is under clinical investigation, with some promising results seen for prepubertal children. Surgically placed silicone implants for cosmetic appearance have also been used with high patient satisfaction. For selected patients, the use of a more noninvasive approach (i.e., cup suction) has been gaining popularity. Regardless of the treatment approach, addressing secondary musculoskeletal findings is commonly employed before and after any intervention.

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467.2 Pectus Carinatum and Sternal Clefts

Steven R. Boas and Catherine Kier

PECTUS CARINATUM

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 four 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.

CLINICAL MANIFESTATIONS

In early childhood, symptoms appear minimal. School-age children and adolescents commonly complain of dyspnea with mild exertion, decreased endurance with exercise, and exercise-induced wheezing. The incidence of increased respiratory infections and use of asthma



Fig. 467.1 Pectus excavatum in a 15-yr-old male. Note the presence of protracted shoulders, inferior rib flares, and sternal depression.

medication is higher than in nonaffected individuals. On physical examination, a marked increase in the anteroposterior chest diameter is seen, with a resultant reduction in chest excursion and expansion (Fig. 467.2). Spirometry has demonstrated both restrictive and obstructive patterns, although the majority of individuals have normal values. Increases in residual volume are often present and result in tachypnea and diaphragmatic respirations. Exercise testing shows variable results. Chest radiographs show an increased anteroposterior diameter of the chest wall, emphysematous-appearing lungs, and a narrow cardiac shadow. The pectus severity score (width of chest divided by distance between sternum and spine; analogous to the Haller index) is reduced.

TREATMENT

For symptomatic patients with pectus carinatum, minimally invasive surgical correction procedures may result in an improvement of the clinical symptoms. Many surgeons prefer to use **bracing techniques** as a first-line treatment, especially for younger patients. Although surgery is performed for some individuals who are symptomatic, it is often performed for cosmetic and psychologic reasons.

STERNAL CLEFTS

Sternal clefts are rare congenital malformations that result from the failure of the fusion of the sternum during the eighth week of gestation. No familial predisposition has been described. Sternal clefts occur in less than 1% of all chest wall deformities. Sternal clefts are classified as partial or complete. Partial sternal clefts are more common and may involve the superior sternum in association with other lesions, such as vascular dysplasias and supraumbilical raphe, or the inferior sternal clefts, which are often associated with other midline defects (pentology of Cantrell). Complete sternal clefts with complete failure of sternal fusion are rare. These disorders may also occur in isolation. The paradoxical movement of thoracic organs with respiration may alter pulmonary mechanics. Rarely, respiratory infections and even significant compromise result. Surgery is required early in life before fixation and immobility occur.

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Fig. 467.2 Pectus carinatum in a 13-yr-old male. Note the central sternal prominence.

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 have been tried. Rib-expanding (vertical expandable prosthetic titanium rib [VEPTR]) procedures have resulted in improved survival (Fig. 467.3).

PROGNOSIS

For some children with asphyxiating thoracic dystrophy, improvement in the bony abnormalities occurs with age. However, children younger than age 1 year often succumb to respiratory infection and failure. Progressive renal disease often occurs in older children. Use of vaccines for influenza and other respiratory pathogens is warranted, as is the aggressive use of antibiotics for respiratory infections.

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467.3 Asphyxiating Thoracic Dystrophy (Thoracic-Pelvic-Phalangeal Dystrophy)

Steven R. Boas and Catherine Kier

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 characteristic skeletal abnormalities as well as variable involvement of other systems, including renal, hepatic, neurologic, pancreatic, and retinal abnormalities (see Chapter 741).

467.4 Achondroplasia

Steven R. Boas and Catherine Kier

Achondroplasia is the most common condition characterized by disproportionate short stature (see Chapter 737). 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 are caused by pathogenic variants in the gene coding for fibroblast growth factor receptor type 3) and how to minimize its serious complications.

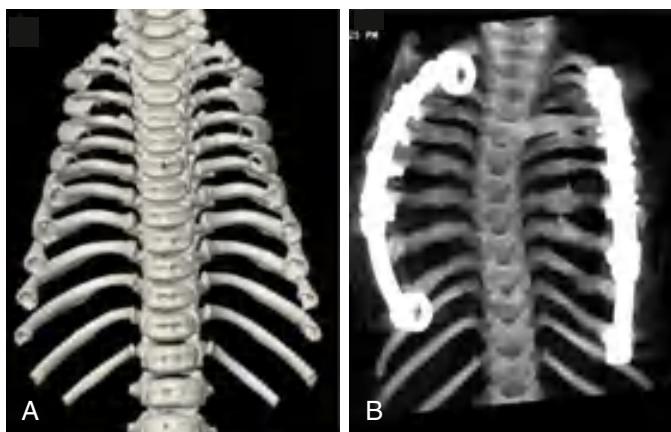


Fig. 467.3 A, Seven-mo-old with Jeune syndrome preoperatively. B, 18 mo after VEPTR insertion. (From Mayer OH. Chest wall hypoplasia—principles and treatment. *Pediatr Respir Rev.* 2015;16:30–34, Fig. 3.)

CLINICAL MANIFESTATIONS

Restrictive pulmonary disease, affecting <5% of children with achondroplasia who are younger than 3 years, 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 hypopneas. Hypoxemia during sleep is a common feature. Risk of airway malacia is greater than the general population. 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 years 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.

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 because of 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 31). 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.

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467.5 Kyphoscoliosis: Adolescent Idiopathic Scoliosis and Congenital Scoliosis

Steven R. Boas and Catherine Kier

Adolescent idiopathic scoliosis (AIS) is characterized by lateral bending of the spine (see Chapter 720). It commonly affects children during

their teen years and during periods of rapid growth. The cause is unknown. Congenital scoliosis is uncommon, affecting females more than males, and is apparent in the first year of life (see Chapter 720.2).

CLINICAL MANIFESTATIONS

The pulmonary manifestations of scoliosis may include chest wall restriction, leading to a reduction in total lung capacity, abnormal gas exchange, airway obstruction, and hypoinflation with associated atelectasis. 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, non-thoracic curves. Respiratory compromise is often more severe in children younger than 5 years 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 20 years old. Children with severe scoliosis (Cobb's angle >70 degrees), especially males, 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 the 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, physical therapy, 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.

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467.6 Congenital Rib Anomalies

Steven R. Boas and Catherine Kier

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 second to fifth 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 used to correct associated chest wall anomalies with rib abnormalities. Adolescent girls with congenital rib anomalies may require cosmetic breast surgery.

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Table 468.1 Indications for Long-Term Mechanical Ventilation

PULMONARY/ALVEOLAR

Bronchopulmonary dysplasia (BPD)
Severe acquired lung disease, such as after pediatric acute respiratory distress syndrome (PARDS)
Pulmonary fibrosis syndromes

AIRWAY

Severe tracheomalacia
Severe bronchomalacia
Obstructive sleep apnea (OSA)
Storage diseases

CHEST

Kyphoscoliosis
Skeletal dysplasias
Obesity

NEUROMUSCULAR

Spinal muscular atrophy
Spinal cord injury
Diaphragmatic dysfunction
Mitochondrial diseases

CENTRAL NERVOUS SYSTEM (CNS)

Congenital central hypoventilation syndrome (CCHS)
Rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysfunction (ROHHAD)
Severe ischemic brain injury
Myelomeningocele with Arnold-Chiari type II malformation
Acquired hypoventilation syndromes

Chapter 468

Chronic Respiratory Insufficiency

468.1 Chronic Respiratory Failure and Long-Term Mechanical Ventilation

Denise M. Goodman and Steven O. Lestrud

Care has improved for the growing population of children with chronic respiratory failure requiring invasive (ventilation through a tracheostomy) and noninvasive (mask ventilation) ventilation, including those with predisposing conditions such as acute respiratory failure, prematurity, and neuromuscular disease. Although it is difficult to determine the prevalence of chronic ventilation, estimates range from approximately 4–6/100,000 children, or 3,000–4,000 children nationally who receive home ventilation. There may be roughly three times more children receiving mask ventilation than invasive mechanical ventilation. The conditions leading to the need for home ventilation are diverse. About 65% of children have a primary neurologic indication, including neuromuscular weakness or abnormal ventilatory control, and ~30% have chronic lung disease (Table 468.1).

Patients with primarily pulmonary indications have a greater likelihood of ultimately being weaned from the need for ventilation than do those with neuromuscular or central nervous system disease. Mortality for patients requiring chronic ventilation is ~12–34%, depending on underlying disease. The lower mortality range is for children with neonatal lung disease, with the higher value for children with complex congenital heart disease. Approximately 12–40% of children are eventually weaned from ventilation and decannulated, reflecting the underlying cause for which ventilation is required. This can usually be accomplished within the first 5 years of life. Nonetheless, the care of these children can be challenging. One study reported that

up to 40% of chronically ventilated children are readmitted within the first year of discharge, usually within the first 3 months. Children requiring long-term mechanical ventilation (LMV) benefit from comprehensive care coordination incorporating generalists, specialists, home nursing, therapies, and a durable medical equipment (DME) resource.

MODALITIES FOR RESPIRATORY SUPPORT

The goals of home mechanical ventilation are to maintain adequate oxygenation and ventilation, minimizing metabolic demands of chronic respiratory failure to ensure adequate somatic growth and optimal developmental gains.

Invasive Positive Pressure Ventilation

The term *invasive* designates ventilation through a tracheostomy. Some devices are suitable for both noninvasive positive pressure ventilation (NPPV) and invasive ventilation, whereas other devices are suitable for only one approach. The ideal home ventilator is lightweight, portable, and quiet. All home ventilators differ from hospital-based ventilators in that air movement is affected either by a piston or turbine that is electrically controlled. This contrasts with hospital ventilators, which are often gas-driven. A home ventilator should be able to provide continuous flow and have a wide range of settings (particularly for pressure, volume, pressure support, and rate) that allows ventilatory support from infancy to adulthood. Battery power for the ventilator, both internal and external, should be sufficient to permit unrestricted portability in the home and community. The equipment must also be impervious to electromagnetic interference and must be relatively easy to understand and troubleshoot.

Although families and care teams may at first resist placement, a **tracheostomy** has several advantages. It provides a secure and stable airway, a standardized interface for attaching the ventilator circuit to the patient, and the ability to easily remove airway secretions and deliver inhaled medications. Pediatric tracheostomy tubes typically have a single lumen and may have an inflatable cuff. Tracheostomy tubes with and without cuff inflation should be sized to control the

air leak around the tube and promote adequate gas exchange, yet allow enough space around the tube to facilitate vocalization and prevent tracheal irritation and erosion from the tube. The child's caregivers need to learn stoma care, elective and emergent tracheostomy changes, proper securing of the tube, suctioning of secretions, and recognition of emergencies such as tube obstruction or decannulation.

Optimal Ventilator Support

Factors such as underlying neuromuscular disease; medications such as sedatives, analgesics, steroids, and muscle relaxants; and prolonged immobility, as well as use of mechanical ventilation, may decondition the respiratory muscles and the diaphragm, resulting in muscle weakness. Consequently, it is important to avoid 24 hour a day patient synchrony with ventilation and titrate the amount of ventilator support to prevent fatigue yet facilitate spontaneous breathing. While assessing ventilator needs, frequent evaluation of gas exchange is needed and can usually be done noninvasively. Ventilator settings should be stable for a given period, dictated by the severity of pulmonary disease, before discharge home.

OTHER MANAGEMENT CONSIDERATIONS

Airway Clearance

One of the most important considerations is maintenance of airway patency. Adequate removal of secretions may minimize intercurrent pulmonary infections. In turn, infections may cause a transient increase in secretions, requiring an escalation of clearance strategies. If the child has an adequate cough, then periodic suctioning may be all that is needed. Some children, however, need additional help mobilizing and clearing secretions. This becomes particularly important in children with neuromuscular disease, for whom regularly scheduled clearance therapies are an imperative. **Vest therapy** (high-frequency chest wall oscillation) uses an inflatable vest that encircles the chest. Air inflates and deflates the vest with phasic pulses against the chest wall, loosening secretions. This device still requires a preserved and strong enough cough to expel secretions. The **cough assist** device provides more active airway clearance, delivering a forceful positive pressure adjunct during inspiration and active negative pressure during expiration. Thus the cough is more effective because of the rapid pressure changes. The cough assist can be used with an artificial airway or mask. Controls will set the inspiratory and expiratory pressures and periods.

Inhalation Medications

Clearance of secretions may be promoted with delivery of hypertonic (3% saline) nebulizations. These are often timed to cough-assist sessions to maximize the clearance benefits of both. Children requiring ventilation also commonly need bronchodilators.

Mucolytics and Anticholinergics

Some patients may need additional interventions as a result of excess secretions. Anticholinergic drugs, principally glycopyrrolate, are often effective, but must be dosed carefully to avoid thickening secretions excessively, which can lead to inspissated secretions and life-threatening plugging of the airway. Oral secretions are sometimes amenable to localized injection of botulinum toxin or select surgical ligation of salivary ducts. It is also wise to ensure that the patient is adequately hydrated, as dehydration may produce thick tenacious secretions. At times a mucolytic may be used. Hypertonic saline is the most common mucolytic, but a number of other agents have been tried, such as dornase alfa and *N*-acetylcysteine.

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 O₂ saturation and heart rate is recommended during sleep and either continuous or intermittent monitoring during the daytime, depending on patient stability. Patients with congenital central hypoventilation syndrome (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 O₂ saturation.

Supplemental Oxygen

Supplemental oxygen may be delivered from a tank or concentrator. Whether on room air or oxygen at baseline, even mild intercurrent infections may lead to an increase in oxygen requirement. In these situations, the child should be evaluated in person rather than over the phone to ensure that a more serious illness is not developing.

Physical, Occupational, and Speech Therapy

The technology needed to support physical well-being should not overshadow the inherent needs common to all children—to play, grow, develop, and interact. Ongoing physical therapy, occupational therapy, and speech therapy can help a child reach full potential, and many achieve complete catch-up development. Early intervention programs and access to play groups are important factors to attaining cognitive and social milestones. When typical development is not attainable, therapies can improve mobilization and muscle strength. Core trunk and abdominal strength is particularly important for pulmonary rehabilitation and essential for successful weaning off ventilation. Other important skills include 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 used for communication because of delayed speech or hearing loss. Audiology specialists should be involved in the assessment of hearing because there is a higher incidence of hearing loss in patients undergoing long-term ventilation.

PREPARING FOR DISCHARGE

A number of threads need to come together for a safe and effective discharge, including medical stability, family education, financial support (insurance or a state waiver program), availability of a DME company, and, when appropriate, home private-duty nursing. A poor outcome may occur with any of the many medical or process factors or family factors, including not only education but also home readiness and psychosocial supports. A standardized discharge process can ensure that all details are addressed, minimizing length of stay and improving safety. An awake and attentive trained caregiver should be in the home of a child with invasive ventilation at all times; this expectation may differ for those receiving NPPV depending on clinical circumstance. For those receiving invasive ventilation, the caregiver may be a nurse, but nursing resources are often scarce, so many programs require two trained family caregivers. The training given to the family includes tracheostomy stoma care, suctioning, equipment expertise, administration of medications, and facility with other devices, such as gastrostomy tubes. In addition, the family is instructed in emergency preparedness, including what to do for acute changes in clinical status, desaturation, or airway obstruction or decannulation. Cardiopulmonary resuscitation training is essential. Parents also need to be able to travel portably with the child and equipment. A standardized emergency bag containing critical tracheostomy and ventilator supplies should accompany the child at all times. Other preparations center around home readiness, including accessibility (number of stairs, if any), members of the household, assuring no smoking in the home, and notification of utility companies such as the electric or heating company to ensure the home is serviced quickly in the event of power interruption. The family must also have a functioning telephone to ensure adequate accessibility and communication between the family and care team. For those going home with invasive mechanical ventilation, both a primary and backup ventilator may be needed, as well as batteries, a self-inflating bag and mask, suctioning equipment, supplemental oxygen, and appropriate monitoring, including a pulse oximeter. The use of high-fidelity

simulation as a means to rehearse skills is increasing. Family training often culminates in an autonomous 24-hour stay *in the hospital* during which time one caregiver must continuously remain awake, and all cares, including ventilator checks, suctioning, tracheostomy tube changes, medications, and the like, are provided by the family.

CARE BY THE GENERAL PEDIATRICIAN

See Chapter 468.4.

Nutrition

Ventilated patients may have nutritional needs that are equal to, greater than, or lesser than those of comparably aged well children. Growth should be tracked at each well child and subspecialty visit. Excessive growth is as harmful as inadequate growth, and excess calories may lead to increased carbon dioxide (CO_2) production. Anthropometry or measured energy expenditure may be needed to assure a more precise prescription of nutritional support. Many children with tracheostomies have oral aversion and/or dyscoordination of swallowing, with resultant risk for aspiration. In these children a gastrostomy tube may ensure adequate nutrition in the interim, while ongoing speech therapy promotes oral feeding.

Infections

Tracheitis (see Chapter 433.2), bronchiolitis (see Chapter 439), and pneumonia (see Chapter 449) 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, along with 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. Colonization may also be distinguished from infection in that colonization usually has few, if any, white blood cells on Gram stain of 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. At times an inhaled antibiotic such as tobramycin might avert progression of 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. Clinical decisions will be based on the child's appearance, any increased need for ventilation or supplemental oxygen, and consultation with the subspecialist. A final caveat is that if a respiratory viral panel is desired, this must be obtained from nasal secretions similar to a well child; tracheal aspirate does not provide an appropriate specimen.

CARE BY THE SUBSPECIALTY TEAM

Weaning Off of the Ventilator

Typically, the ventilator settings are reduced, minimizing ventilator parameters to achieve physiologic respiratory rates and 6–8 mL/kg tidal volumes. Subsequent maneuvers will evaluate the patient free breathing, initially with simple observed transition times of 5–10 minutes, extending time off as clinically indicated. This can be done in the outpatient setting during visits with the pulmonologist or other subspecialist responsible for ventilator management. 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 hours nightly during sleep, a polysomnogram study performed off the ventilator may be considered before complete liberation from the

mechanical ventilation device. Successful liberation from mechanical ventilation, if it occurs, often takes place between the ages of 2 and 5 years. One thought is that with ambulation and development of core strength, respiratory reserve improves, facilitating weaning. Even so, residual lung disease is common. Children with a history of bronchopulmonary dysplasia (BPD) and previous ventilator dependence often have significant airway obstruction on pulmonary function testing.

PSYCHOSOCIAL CONSIDERATIONS

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 routines, priorities, and overall lifestyle and may adversely affect relationships both within the family and with extended family and friends. Practical considerations include loss of spontaneity in family outings, sleep disturbance, extra expenses, having strangers in the house providing care, and adhering to medical regimens and follow-up visits. Intangible stresses are also prominent, including disruption in the usual parent-child caregiving roles and stresses between parent partners and with other children. The loss of normality, sense of isolation, and concerns regarding what is best for the child are additional sources of distress. All of these stresses are exacerbated by challenges in securing reliable home private-duty nurse resources; this issue may delay hospital discharge and complicate postdischarge care, at times even leading to readmission because of lack of adequate support. For children with a life-limiting condition, there is the additional need to periodically revisit the child's current medical state, sense of well-being, and trajectory of illness, as critical decisions will eventually arise regarding end-of-life care. The general pediatrician can often be a familiar and comfortable safe place to explore these issues, as parents may be conflicted in wanting to be a "good" parent while feeling guilty about their own needs and vulnerabilities. Finally, families may find transportation to frequent outpatient visits difficult; telemedicine may offer an alternative for select situations.

ADULT TRANSITION

There are a growing number of children surviving into adulthood who require chronic ventilation. There are little empiric data regarding this transition, including identifying patients for whom transition is appropriate, implementing a standardized transition process, partnering with adult pulmonologists, or replicating in an adult environment the care coordination provided by the pediatric care team. The pulmonary team ideally initiates ongoing discussions regarding self-care responsibilities and transitioning of medical care to adult providers with the adolescent and his or her 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 years and includes referral to an internist and 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.

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468.2 Congenital Central Hypoventilation Syndrome

Amy Zhou, Susan M. Slattery, Casey M. Rand, and Debra E. Weese-Mayer

CCHS is a clinically complex *neurocristopathy* that includes a variable severity of respiratory and autonomic dysregulation, as well as Hirschsprung disease and neural crest tumors in a subset of patients. In the classic CCHS presentation, symptoms of alveolar hypoventilation manifest in the newborn period and during sleep only—with

Table 468.2 Clinical Manifestations of CCHS

ORGAN SYSTEM	CLINICAL MANIFESTATIONS
Ophthalmologic	Decreased/absent pupillary light response Anisocoria Strabismus Lack of convergent gaze Marcus Gunn jaw winking
Respiratory	Alveolar hypoventilation Absent perception of dyspnea
Cardiovascular	Bradycardia Prolonged sinus pauses (>3 seconds) Transient asystole Decreased heart rate variability Low normal daytime blood pressure Orthostatic hypotension Nondipping blood pressure circadian pattern Decreased BP response to exercise Syncope
Gastrointestinal	Hirschsprung disease (20%) Constipation Esophageal dysmotility
Endocrine	Hyperinsulinism Hypoglycemia Hyperglycemia
Neurologic	Decreased anxiety Decreased pain perception Seizures Neurocognitive deficits
Skin	Sporadic profuse sweating
Tumors	Neuroblastoma Ganglioneuroma Ganglioneuroblastoma
Others	Decreased baseline body temperature Poor heat tolerance

CCHS, Congenital central hypoventilation syndrome; BP, blood pressure; GI, gastrointestinal.

From Bishara J, Keens TG, Perez IA. The genetics of congenital central hypoventilation syndrome: clinical implications. *Am J Med Genet*. 2018;11:135–144, Table 1. Originally published by and used with permission from Dove Medical Press Ltd.

diminished tidal volume and a typically monotonous respiratory rate leading to cyanosis and hypercarbia. In more **severe** cases of CCHS, the hypoventilation manifests during wakefulness and sleep. In the **later-onset** cases of CCHS (**LO-CCHS**), onset of overt symptoms is delayed until 1 month of age or older (often into childhood and adulthood). Hypoventilation is typically during sleep only and usually milder in LO-CCHS. CCHS and LO-CCHS are further characterized by partial to complete failure of peripheral and central chemoreceptors to properly respond to hypercarbia and hypoxemia during wakefulness and sleep, coupled with physiologic and/or anatomic autonomic nervous system (ANS) dysregulation (ANSD). Physiologic dysregulation may include all organ systems affected by the ANS, specifically the respiratory, cardiac, sudomotor, vasomotor, ophthalmologic, neurologic, and enteric systems (Table 468.2). The anatomic or structural ANSD includes Hirschsprung disease and tumors of neural crest origin (neuroblastoma, ganglioneuroma, or ganglioneuroblastoma).

GENETICS

The *PHOX2B* gene is the disease-defining gene for CCHS. *PHOX2B* encodes a highly conserved homeodomain transcription factor, is essential to the embryologic development of the ANS from the neural crest, and is expressed in key regions and systems that explain much

of the CCHS phenotype. Individuals with CCHS are *heterozygous* for either a **polyalanine repeat expansion pathogenic variant (PARPV)** in exon 3 of the *PHOX2B* gene (normal number of alanines is 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 **nonpolyalanine repeat expansion pathogenic variant (NPAPRV)** resulting from a missense, nonsense, frameshift, stop codon, in-frame indels (in-frame insertions, deletions, or duplications), full exon/gene deletions, or splice-site pathologic genetic variant. Approximately 90–92% of cases of CCHS have PARPVs and the remaining 8–10% of cases have NPAPRVs (Table 468.3).

Stepwise clinical *PHOX2B* testing for probands with the CCHS phenotype is advised. **Step 1:** *PHOX2B* screening test (fragment analysis), then if negative; **Step 2:** *PHOX2B* sequencing test, then if negative; **Step 3:** *PHOX2B* multiplex ligation-dependent probe amplification (MLPA) test to minimize the risk of false-negative findings, minimize the expense and need for more than one blood sample, and expedite confirmation of the diagnosis.

Genetic counseling is essential for family planning and for delivery room preparation in anticipation of a CCHS birth and ensuring adequate ventilation for the mother during pregnancy. *PHOX2B* testing is also advised for both parents of a child with CCHS to anticipate the risk of recurrence in subsequent pregnancies (if mosaic) and to determine if a parent has yet-undiagnosed LO-CCHS. Fragment analysis *PHOX2B* testing (also known as the *screening test*) will best identify low-level somatic mosaicism. Prenatal testing for a *PHOX2B* variant is clinically available (www.genetests.org) for families with a known *PHOX2B* gene variant.

Ventilator Dependence and Control of Breathing

Patients with CCHS have deficient CO₂ 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 hypoventilation 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, which can result in respiratory failure, does not consistently improve with advancing age. A subset of older children with CCHS may show an increase in ventilation (specifically an increase in respiratory rate rather than an increase in tidal volume) when they are exercised at various work rates. This response is possibly secondary to neural reflexes from rhythmic limb movements, although an increase in minute ventilation is often insufficient to avoid physiologic compromise.

The greater the number of extra alanines, the more likely the need for continuous ventilatory support, at least among the most common *PHOX2B* PARPV genotypes (20/25, 20/26, 20/27). Although *PHOX2B* genotype seems to anticipate the severity of hypoventilation, it does not correlate with exogenous ventilatory challenge responses. Infants and young children as a group have reasonable ventilatory response slopes while awake, but this advantage seems to vanish by school age.

Hirschsprung Disease (see Chapter 378.4)

Overall, 20% of children with CCHS also have Hirschsprung disease (HSCR), known as *Haddad syndrome*, and any infant or child with CCHS who presents with constipation should undergo rectal biopsy to screen for the absence of ganglion cells. The frequency of Hirschsprung disease seems to increase with the longer polyalanine repeat tracts (genotypes 20/27–20/33) and in those with NPAPRVs. Even in cases without frank HSCR disease, individuals with CCHS may display symptoms of gastrointestinal abnormalities such as severe constipation and abnormal esophageal motility, suggesting ganglion cell dysfunction.

Table 468.3 Congenital Central Hypoventilation Syndrome–Related Symptoms by PARPV vs NPARPV and PARPV Genotype

FEATURE	GENOTYPE					
	PARPV GENOTYPE			NPARPV		
	20/24 ¹ , 20/25	20/26	20/27	NPARPV IN GENERAL	38BP DELETION	
Respiratory (hypoventilation)	Asleep only	Awake with exertion and eating and asleep	Awake and asleep	Awake and asleep	Awake and asleep	
Cardiac arrhythmia: Abrupt sinus pauses ≥3 seconds warranting cardiac pacemaker	Variable: None with childhood onset; a subset will have prolonged sinus pauses in adulthood	19%	>80%	None with childhood onset to date		
Hirschsprung disease	<0.1%	20–30%	30%	80–90%	95–100% severe long segment disease (i.e., entire colon and some small intestine)	
Severe constipation		~50+%	~50+%			
Esophageal dysmotility/dysphagia		First year of life	First year of life			
Neural crest tumors	Neuroblastoma Ganglioneuroblastoma Ganglioneuroma	0% 0% 0%	0% 0% 0%	See footnote 2 0% 0%	50% <5% <5%	
ANSO: Pupillary response to light	Normal response	Midsize pupils with attenuated response to light	Small pupils at rest; nearly absent response to light	Large pupils at rest; negligible response to light		

ANSO, Autonomic nervous system dysregulation; NPARPV, nonpolyalanine repeat expansion pathogenic variant (i.e., missense, nonsense, frameshift, stop codon, splice site); PARPV, polyalanine repeat expansion pathogenic variant.

1. Genotype 20/24 would be considered a susceptibility allele (needs another factor to manifest) or a low- or variable-penetrance allele with features that can be triggered by pharmacologic agents (a pharmaco-genetic phenomenon) or a gene × environment interaction (without main effects).

2. Generally 0%; however, an infant with the 20/33 genotype had metastatic neuroblastoma (12).

From Weese-Mayer DE, Rand CM, Khaytin I, et al. Congenital central hypoventilation syndrome. Updated 2021 Jan 28. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from <https://www.ncbi.nlm.nih.gov/books/NBK1427/>. Table 2, pp. 7–8.

Tumors of Neural Crest Origin (see Chapter 547)

Tumors of neural crest origin are more frequent in patients with NPARPVs (50%) than in those with PARPVs (1%). These extracranial tumors are more often neuroblastomas in individuals with NPARPVs, but ganglioneuromas and ganglioneuroblastomas occur in a small subset of patients.

Cardiac Asystoles

Transient, abrupt, and prolonged sinus pauses have been identified in patients with CCHS, necessitating implantation of cardiac pacemakers when the pauses are ≥3 seconds. Among patients with the most common *PHOX2B* genotypes, 19% of those with the 20/26 genotype and 83% of those with the 20/27 genotype have cardiac pauses of 3 seconds or longer. The risk for sinus pauses among children with NPARPVs is unknown at present.

Heart rate variability is characteristically decreased in CCHS, likely because of reduced cardiac baroreflex sensitivity and blunted

sympathetic response. One report demonstrated a genotype–phenotype relationship for heart rate variability during exogenous ventilatory response testing, prompting assessment of risk for sinus pauses. Introduction of 72-hour Holter recordings every 12 months, at a minimum, has allowed for early identification of these abrupt sinus pauses, permitting timely cardiac pacemaker implantation.

Autonomic Nervous System Dysregulation

A higher number of polyalanine repeats on the affected allele among patients with a PARPV is associated with an increased number of physiologic symptoms of ANSD. 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, altered vasomotor tone, and altered pain and anxiety perception.

Characteristic Facial Morphology

Characteristic facial features have been described for children with CCHS. Using facial photogrammetry, five features were used to correctly predict 86% of CCHS cases and 82% of controls in a matched case control study. A typical CCHS face is characterized by an upper and midface that is short relative to its width, resulting in a characteristic broad, flat, boxlike appearance (Fig. 468.1). The lateral one third of the upper lip vermillion border is overturned so it is flesh-colored instead of pink. Results also suggest that male CCHS patients are more strongly affected than females.

Neuropathology

Brain imaging studies and functional MRI (fMRI) responses have identified structural anomalies in CCHS cases that may contribute to the observed respiratory and autonomic phenotypes. These findings may be primarily the result of *PHOX2B* variant-induced failure of neurogenesis in the human embryo, but a significant contribution from postnatal hypoxic, hypercarbic, or perfusion damage cannot be excluded. 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. The following regions pertinent to respiratory control in the pons and medulla of the brainstem show *PHOX2B* expression: locus coeruleus, dorsal respiratory group, nucleus ambiguus, and 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.

CLINICAL MANIFESTATIONS

Patients with CCHS usually present with symptoms in the first few hours after birth. Most children are the products of uneventful pregnancies and are term infants with appropriate weight for gestational age. Variable Apgar scores have been reported. The affected infants do not show signs of respiratory distress, but their shallow respirations and respiratory pauses (apnea) usually evolve to respiratory failure with apparent cyanosis in the first days of life. In neonates with CCHS, 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 when multiple attempts at extubation fail in an intubated neonate who appears well with ventilatory support but develops respiratory failure without respiratory distress after removal of the support. However, more severely affected infants with CCHS hypoventilate awake



Fig. 468.1 Characteristic CCHS facies. Photographs of representative CCHS. These two children with CCHS both have the representative facies. The female with CCHS (A) has a *PHOX2B* genotype of 20/25, and the male with CCHS (B) has a 20/27 genotype. Note the decreases in sloping of the forehead, upper face height, upper facial inclination, nasolabial angle, upper and lower lip heights, and the inferior inflection of the lateral vermillion border of the upper lip. (Modified from Todd ES, Weinberg SM, Berry-Kravis EM, et al. Facial phenotype in children and young adults with *PHOX2B*-determined congenital central hypoventilation syndrome: quantitative pattern of dysmorphology. *Pediatr Res.* 2006;59:39–45, Fig. 2A and 2C.)

and asleep; thus the previously described difference in Paco_2 between states may not be apparent. Often, the respiratory rate is higher in rapid eye movement (REM) sleep than in non-REM sleep in individuals with CCHS, and in general, respiratory rates are higher in infants and children with CCHS than similarly aged peers with intact control of breathing.

LO-CCHS should be suspected in infants, children, and adults who have unexplained centrally mediated hypoventilation and/or seizures or cyanosis, especially subsequent to the use of anesthetic agents and/or sedation, acute respiratory illness or recurrent severe respiratory illness with difficulty weaning from ventilator support (and failed extubations), and potentially obstructive sleep apnea (OSA) unresponsive to traditional intervention. These individuals may have other evidence of chronic hypoventilation, including pulmonary hypertension, polycythemia, elevated bicarbonate concentration, difficulty concentrating, and mild unexplained neurocognitive impairment. A heightened level of suspicion has led to increasing numbers of older children and adults diagnosed with LO-CCHS receiving proper treatment. This later presentation reflects the variable penetrance of a subset of *PHOX2B* variants and the potential role of an exogenous cofactor in unmasking the hypoventilation phenotype.

In addition to treatment for the alveolar hypoventilation, children with CCHS require comprehensive physiologic evaluation during sleep and wakefulness, including age-appropriate activities of daily living such as eating, as their hypoxemia and hypercarbia from insufficient artificial ventilation may go unnoticed. It is necessary to provide coordinated care to optimally manage associated multisystem abnormalities such as Hirschsprung disease, tumors of neural crest origin, and symptoms of physiologic ANSD, including cardiac asystole, among other findings (details provided in American Thoracic Society [ATS] 2010 Statement on CCHS) (Table 468.4).

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 symptoms characteristic of CCHS (Table 468.5). The availability of clinical *PHOX2B* genetic testing allows for early and definitive diagnosis of CCHS (see Table 468.3). Because individual subfeatures of CCHS mimic many treatable and/or genetic diseases, the following disorders should also be considered: altered airway or intrathoracic anatomy (diagnosis made with bronchoscopy and chest CT), diaphragm dysfunction (diagnosis made with diaphragm fluoroscopy), 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, profound hypercarbia without respiratory distress during sleep will quickly lead the clinician to consider the diagnosis of CCHS or LO-CCHS.

MANAGEMENT

Supported Ventilation: Diaphragm Pacing

Depending on the severity of the hypoventilation, the individual with CCHS can have various options for artificial ventilation: positive pressure ventilation (noninvasive via mask or invasive via tracheostomy) or negative pressure ventilation (pneumosuit, chest cuirass, or diaphragm pacing). Chronic mechanical ventilation is addressed in Chapters 468.1 and 468.4. Diaphragm pacing offers another mode of supported ventilation, involving bilateral thoracoscopic 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 to the phrenic nerve to stimulate contraction of the diaphragm. A tracheostomy is typically required, because the pacers induce a negative pressure on inspiration as a result of the contraction of the diaphragm being unopposed by pharyngeal dilatation, resulting

Table 468.4 Recommended Evaluations in Patients with CCHS

EVALUATION	FREQUENCY	PHOX2B GENOTYPE	
Pulmonary	Comprehensive physiologic testing during sleep and wakefulness, including continuous pulse oximetry, cardiorespiratory monitoring, capnography, and polysomnography	<3 yr of age: every 6 mo ≥3 yr: annually	All PHOX2B PARM and NPARM
Cardiovascular	Ambulatory cardiac monitoring (≥72 hr), blood pressure, and echocardiogram	Annually	All PHOX2B PARM and NPARM
Gastrointestinal	Barium enema or anorectal manometry; confirmation by rectal biopsy	At initial diagnosis and subsequently if symptoms appear	20/26-20/33 PARM and NPARM
Neurodevelopmental	Comprehensive neurocognitive tests	<3 yr of age: every 6 mo ≥3 yr: annually	All PHOX2B PARM and NPARM
Oncologic	Chest radiograph, abdominal ultrasound, and urine catecholamines (homovanillic acid and vanillylmandelic acid)	0-6 yr of age: every 3 mo 6-10 yr of age: every 6 mo >10 yr of age: per oncologist recommendation	20/28-20/33 PARM and NPARM
Ophthalmologic	Comprehensive ocular testing by an ophthalmologist	Annually	All PHOX2B PARM and NPARM

NPARM, Nonpolyalanine repeat expansion mutation; PARM, polyalanine repeat expansion mutation; PHOX2B, paired-like homeobox 2B.

Data from the 2010 American Thoracic Society Statement on CCHS *Am J Respir Crit Care Med.* 2010;181:626-644.

From Kasi AS, Li H, Harford KL, et al. Congenital central hypoventilation syndrome: optimizing care with a multidisciplinary approach. *J Multidisp Healthcare.* 2022;15:455-469, Table 1. Originally published by and used with permission from Dove Medical Press Ltd.

Table 468.5 Differential Diagnoses of Congenital Central Hypoventilation Syndrome

METABOLIC
Mitochondrial defects (e.g., Leigh disease)
Pyruvate dehydrogenase deficiency
Hypothyroidism
NEUROLOGIC
Structural central nervous system abnormalities (e.g., Arnold Chiari malformation, Möbius syndrome)
Vascular injury (e.g., central nervous system [CNS] hemorrhage, infarct)
Trauma
Tumor
PULMONARY
Primary lung disease
Respiratory muscle weakness (e.g., diaphragm paralysis, congenital myopathy, myasthenia gravis)
GENETIC
Prader-Willi syndrome
Familial dysautonomia and other neuropathies
OTHER
Sedative drugs
Rapid-onset obesity, hypothalamic dysregulation hypoventilation, autonomic dysregulation (ROHHAD)

Modified from Healy F, Marcus CL. Congenital central hypoventilation syndrome in children. *Pediatr Respir Rev.* 2011;12:253-263, Table 1.

in airway obstruction with paced breaths. Individuals with CCHS who are ventilator-dependent for 24 hours a 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. In addition, a growing but still limited number of children and adults who require artificial

ventilatory support only during sleep are now using diaphragm pacing. This is likely because of the introduction of thoracoscopic diaphragm pacer implantation and shortened postoperative recovery time. However, in the absence of a tracheostomy, diaphragm pacing during sleep may cause airway obstruction at varied levels of the airway, depending on the specific patient. The potential for these obstructions needs to be carefully considered before diaphragm pacer implantation, and certainly before tracheal decannulation.

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 CCHS individuals lack innate ventilatory and arousal responses to hypoxemia and hypercarbia. In the event of physiologic compromise, other non-CCHS children will show clinical signs of respiratory distress. By contrast, 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 CO₂ monitor, and close supervision of these values by a highly trained registered nurse (RN) in the home and at school. While awake, patients with CCHS themselves are unable to sense or adequately respond to a respiratory challenge that may occur with ensuing respiratory illness, increased exertion, or even the simple activity of eating. At a minimum, it is essential that individuals with CCHS have continuous monitoring with pulse oximetry and end-tidal CO₂ with RN supervision during all sleep time, but ideally 24 hours a day. These recommendations apply to all CCHS and LO-CCHS patients regardless of the nature of their artificial ventilatory support, but especially those with diaphragm pacers, as only the most recent transmitter has mechanical dysfunction alarms intrinsic to the diaphragm pacer device.

Noninvasive Ventilatory Support Equipment

Supplemental oxygen with positive pressure support can be administered by nasal cannula, pillows, nasal mask, or full-face mask via an actual ventilator, but this is suitable only for highly cooperative children with milder hypoventilation during sleep only. Long-term use of mask ventilation in infants and young children may result in

midface dysplasia or pressure wounds. Mask ventilation does not offer the stable airway provided by a tracheostomy with mechanical ventilation, especially in the rapidly developing infant and young child.

Positive Pressure Ventilators

Ideally, a ventilator intended for home use is lightweight and small, quiet so it does not interfere with activities of daily living or sleep, is able to entrain room air, preferably has continuous flow, and has a wide range of settings (particularly for pressure support, pressure, volume, and rate) that allows ventilatory support from infancy to adulthood. Battery power for the ventilator, both internal and external, should be sufficient to permit unrestricted portability in the home and community. The equipment must also be impervious to electromagnetic interference and must be relatively easy to understand and trouble-shoot. Children who are chronically ventilated via positive pressure ventilation will require surgical placement of a tracheostomy tube. The tracheostomy tube provides stable access to the airway, a standardized interface for attaching the ventilator circuit to the patient, and the ability to easily remove airway secretions or deliver inhaled medications. Pediatric tracheostomy tubes typically have a single lumen and may have an inflatable tight-to-the-shaft cuff. Tracheostomy tubes with and without cuff inflation should be sized to control the air leak around the tube and promote adequate gas exchange yet allow enough space around the tube to facilitate vocalization and prevent tracheal irritation and erosion from the tube.

Optimizing Neurocognitive Performance

Impaired oxygen delivery to the brain, whether acute or chronic, can have detrimental effects on neurocognitive development. The ATS statement on CCHS recommends positive pressure ventilation via tracheostomy in the first several years of life to ensure optimal oxygenation and ventilation. The method of choice for respiratory support in later years will depend on a variety of factors, including severity of disease, patient age, level of patient and family cooperation, and availability and quality of home healthcare, among other factors. The level of oxygen stability obtained with each modality varies. Thus the method of respiratory assistance, especially in infancy and early childhood, is likely to play a factor in neurocognitive outcome.

Past literature has indicated reduced neurocognitive performance in school-age children with CCHS, with mean full scale intellectual quotient (IQ) values one standard deviation below the normal IQ of 100. Even in preschool years, children with CCHS and the 20/26 and 20/27 *PHOX2B* genotypes demonstrate reduced neurocognitive performance compared to children with the 20/25 genotype. In these cases, *PHOX2B* genotype is clearly associated with both mental and motor outcomes. An association is also found between IQ and CCHS-related features such as severe cyanotic breath holding spells, sinus pauses, seizures, and severity of hypoventilation. One study reported a negative correlation between neurocognitive performance scores and length of polyalanine expansion, suggesting that both the specific gene variant and ventilatory method may influence neurocognitive outcome. Findings from a neurocognition study in preschool-age children suggest the potential for excellent neurocognitive outcome in some patients with CCHS. Neurodevelopmental monitoring would be most beneficial beginning in early infancy and followed closely with advancing age.

Efforts are underway to evaluate and characterize the CCHS phenotype longitudinally through the International CCHS Registry (<http://clinicaltrials.gov/show/NCT03088020>) (Northwestern University). Delineating markers of disease progression and understanding the clinical manifestations of CCHS with advancing age will provide more accurate guidelines to healthcare providers, allowing physicians, families, and patients to better anticipate healthcare needs of affected individuals and for use as biomarkers for future pharmacologic intervention studies.

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468.3 Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Sarah F. Barclay, Ilya Khaytin, Amy Zhou, Casey M. Rand, and Debra E. Weese-Mayer

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare, poorly understood disorder with childhood onset, the first sign of which is sudden, rapid, and extreme weight gain in a previously healthy child. The acronym describes the presenting symptoms and the typical order in which they will manifest or unfold, as the condition evolves over months to years. Despite its rarity, ROHHAD must be considered whenever rapid-onset obesity is observed in a child, because in the absence of appropriate treatment, a high mortality rate is associated with the severe central hypoventilation that will invariably develop.

The diagnosis is initially considered after the observation of rapid-onset obesity (15-20 lb gain) after age 1.5 years, accompanied by at least one additional sign of hypothalamic dysfunction (HD). Central hypoventilation may not be present at the time of rapid weight gain but will develop over time, and artificial ventilatory support will be required at least during sleep, if not 24 hours a day. Signs of autonomic nervous system dysregulation typically occur after the weight gain, HD, and hypoventilation have been identified. Additionally, approximately 40% of ROHHAD patients will have or develop a tumor of neural crest origin, typically ganglioneuroma or ganglioneuroblastoma (a small number of neuroblastomas have been identified).

ROHHAD is distinct from LO-CCHS (see Chapter 468.2). ROHHAD is primarily distinguished from LO-CCHS by the presence of obesity and other signs of HD and by the absence of a CCHS-related pathogenic *PHOX2B* variant.

CLINICAL MANIFESTATIONS

Children with ROHHAD initially appear healthy, with an unremarkable medical history. The initial symptoms present between ages 18 months and 7 years. Typically, the first symptom observed is rapid-onset obesity, with weight gain of 15-30 lb in 6-12 months. The growth charts from a representative child followed longitudinally illustrate the characteristic accelerated increase in weight and body mass index (BMI) (Fig. 468.2). This is considered one sign of HD in these patients.

The second common sign of HD, seen in most ROHHAD patients, is disordered water balance, including hypernatremia and hyponatremia and both adipsia and polydipsia. Growth hormone (GH) deficiency is also observed in most patients. In some, this manifests clinically as slowed growth rate and short stature, whereas in others a failed GH stimulation test is the only manifestation. Hyperprolactinemia is observed near universally in patients with ROHHAD. Other symptoms of HD, occurring in >25-50% of ROHHAD patients, include poor thermoregulation, central hypothyroidism, central adrenal insufficiency, and delayed or precocious puberty. The number of hypothalamic abnormalities that will be observed and the sequential order in which they will appear are variable, and some symptoms may not manifest for months to 1-2 years after the initial diagnosis. However, all ROHHAD patients will present with at least one of these signs of HD beyond the rapid-onset weight gain.

Sleep-disordered breathing (SDB) is one of the key symptoms of ROHHAD, often manifesting as one of the most severe features of the phenotype, with the greatest potential for severe morbidity and death. More than half of ROHHAD patients have initial obstructive sleep apnea (OSA); although SDB is known to be associated with obesity and OSA is often seen in obese individuals, over time, when the ROHHAD phenotype unfolds, SDB will evolve beyond what could potentially be explained as obesity related. All ROHHAD patients will eventually develop central alveolar hypoventilation, requiring artificial ventilation as life support, even when the upper airway obstruction is relieved as an intervention for OSA. About half of ROHHAD patients will require artificial ventilation only during sleep, whereas half will require

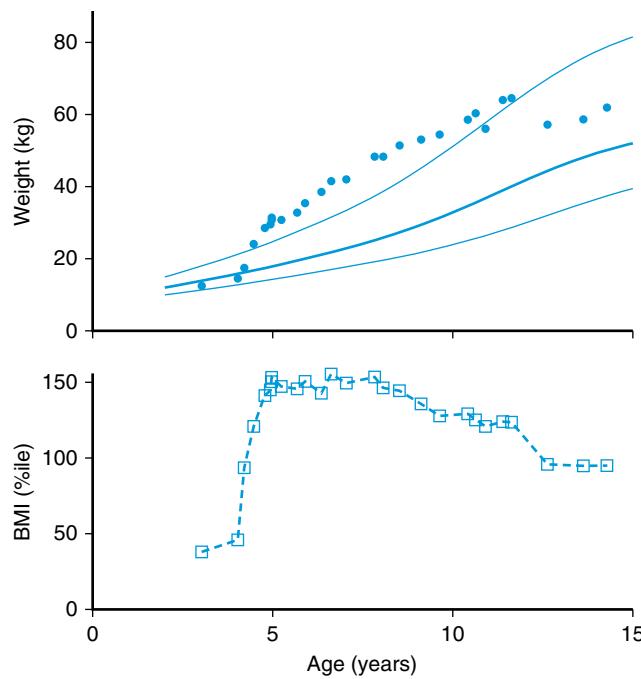


Fig. 468.2 Growth curves of weight and body mass index (BMI) from a child with ROHHAD. Weight and BMI percentiles for a child with ROHHAD from the time of diagnosis until age 14.3 yr, demonstrating the rapid onset of obesity. Weight and BMI percentiles were calculated using published CDC growth charts and methods. Solid lines in weight graph represent 3rd, 50th, and 97th percentiles. Dots and open squares are individual measurements for the child.

continuous artificial ventilation (during sleep and wakefulness). Up to 50% of children with ROHHAD will have a cardiorespiratory arrest before their hypoventilation is identified and treated. Unfortunately, many ROHHAD patients die from cardiorespiratory arrest because of unrecognized or inadequately managed hypoventilation. Thus if a ROHHAD diagnosis is suspected, it is crucial that a comprehensive respiratory physiology evaluation be performed, including overnight polysomnography and awake physiologic recording in activities of daily living and followed serially long after the hypoventilation is identified and intervention provided.

All ROHHAD patients have symptoms of **autonomic nervous system (ANS) dysregulation (ANSD)**; the specific symptoms and the order and timing of their appearance will vary among patients. The most common manifestations of ANSD in ROHHAD are ophthalmologic, including **pupillary dysfunction**, **strabismus**, and **alacrima**. Many ROHHAD patients will have **gastrointestinal dysmotility**, presenting as either chronic constipation or, less commonly, chronic diarrhea. Other signs of ANSD include **altered sweating**, **decreased body temperature**, **decreased sensitivity to pain**, and **cold hands and feet** indicating altered vasomotor tone. **Bradycardia** is observed in some ROHHAD patients, typically related to **extreme hypothermia**.

Neural crest tumors are observed in ~40% of ROHHAD patients, most frequently ganglioneuromas and ganglioneuroblastomas of the chest or abdomen; rarely a neuroblastoma has been reported. These tumors can occur at any age, so proactive imaging evaluation throughout childhood and adolescence to identify the tumors is essential.

Patients do not always have behavioral or psychologic disorders if artificial ventilation is optimized. For those who do, however, the disorders can be quite severe, including anxiety, depression, rage, lethargy, irritability, aggressiveness, psychosis, and obsessive-compulsive disorder. Developmental disorders described include neurocognitive delay, developmental regression, attention-deficit/hyperactivity disorder, and pervasive developmental disorder. These disorders are most likely accentuated by poorly managed

hypoventilation because the majority of ROHHAD patients have no behavioral issues and a normal IQ.

Seizures have been reported in some ROHHAD patients, likely caused by episodes of hypoxemia, when hypoventilation either has not yet been diagnosed or has been inadequately managed.

DIAGNOSIS

The diagnostic criteria for ROHHAD include rapid-onset obesity after 1.5 years of age; central hypoventilation beginning after age 1.5 years; ≥1 of the following signs of HD: disordered water balance, hyperprolactinemia, failed GH stimulation test, central hypothyroidism, corticotropin deficiency, and altered onset of puberty; and features of autonomic dysregulation. Additionally, it must be *confirmed* that no CCHS-related *PHOX2B* pathogenic variant is present to rule out a diagnosis of CCHS or LO-CCHS.

Because no single diagnostic test is currently available for ROHHAD, the diagnosis must be based on observation of the clinical presentation and therefore requires expert consultation in multiple pediatric subspecialties, including respiratory physiology, endocrinology, autonomic medicine, cardiology, oncology, nutrition, critical care, sleep, and psychiatry, with orchestration by the child's pediatrician. When a child with rapid-onset obesity is seen by a general pediatrician or family physician, the steep trajectory of weight gain should signal prompt consideration of a ROHHAD diagnosis, with immediate referral to a center with expertise in this unique constellation of symptoms. Early recognition is critical for a positive outcome in children with ROHHAD. *If alveolar hypoventilation is not identified and aggressively managed, cardiorespiratory arrest can occur and has proved fatal in many cases.*

A characteristic set of facial features has been described for CCHS, which, using facial photogrammetry, is able to identify 86% of genetically confirmed CCHS cases (see Chapter 468.2). Although such formal evaluation of ROHHAD facies has not been completed, a preliminary report indicates that ROHHAD patients have similar facial mapping characteristics to CCHS patients, especially the characteristic “**lip trait**,” in which the lateral one third of the upper vermillion border is flesh-colored instead of pink (Fig. 468.3). This is distinct from the general lip changes observed with increasing BMI in a study of adolescent females, which include fuller-looking lips and downturned corners of the mouth.

Initial evaluations should include overnight polysomnography to identify OSA or central hypoventilation, awake comprehensive physiologic recording in age-appropriate activities of daily living, cardiac evaluation to assess for cor pulmonale and rhythm disturbance, endocrine function evaluation, screening for neural crest tumors (chest radiograph, abdominopelvic ultrasound, or meta-iodobenzylguanidine [MIBG] scan), and a behavioral and psychological evaluation, especially if any behavioral, psychologic, or developmental disorders are seen or suspected. Brain imaging should be performed to rule out intracranial lesions that may account for the observed hypothalamic-pituitary abnormalities (using the hypothalamic-pituitary protocol). If the criteria are met and a ROHHAD diagnosis is made, successful management requires ongoing teamwork among the various subspecialists, with a pediatrician team leader to orchestrate all testing, the family, and the child to provide optimized integrated care for the child.

MANAGEMENT

There is currently no cure for ROHHAD. Rather, treatment consists of early identification, meticulous monitoring, and anticipatory along with symptomatic management of the various phenotypic features as they develop (“unfold”). Comprehensive initial evaluations should determine the nature and severity of hypoventilation, HD, and ANSD, and appropriate interventions should be implemented in a time-sensitive manner. Obesity in ROHHAD is very difficult to control, but in consultation with a nutritionist and endocrinologist, the trajectory of advancing weight gain can be diminished with moderate exercise and calorie restriction, leading to improved BMI with advancing age. Specific signs of HD and ANSD should be evaluated by a pediatric endocrinologist and expert in pediatric autonomic medicine, respectively, and treated as necessary longitudinally as the phenotype



Fig. 468.3 Characteristic CCHS “lip trait” shown in a child with ROHHAD. Shown here is the mouth of a child with ROHHAD at age 4 (A) and 11 (B) years. The lateral one third of the upper vermillion border is flesh-colored instead of pink. This is not a characteristic feature of obese faces in general (the upper lip is neural crest in origin).

“unfolds” and “refolds.” Such treatments or management strategies may include hormone replacement; regimented fluid intake; ophthalmologic assessment and treatment; longitudinal monitoring of peripheral, core, and ambient temperature; and management of constipation with stool softeners. Disordered water balance to prevent dehydration should be addressed, as well as regulation of heart rate, because bradycardia is seen in some patients (usually with decreased core temperature), though cardiac pacemakers are rarely indicated.

Neural crest tumors should be assessed and resected by a pediatric surgeon together with a pediatric oncologist, because the sheer size of these benign tumors creates serious compromise to surrounding tissues. If no tumor is identified initially, screening should continue every 6 months until adulthood, because a malignant neuroblastoma has been identified in an adolescent ROHHAD patient.

Most critical is the management of hypoventilation. Initial intervention for OSA will likely involve surgical relief of the upper airway obstruction. This will usually unveil central hypoventilation, and initiation of supported ventilation will be required. If no central hypoventilation is identified, the patient should continue to be vigilantly monitored by a respiratory physiologist because all ROHHAD patients will eventually develop central hypoventilation requiring artificial ventilation during sleep at a minimum. Individuals with ROHHAD have attenuated to absent physiologic responsiveness to hypoxemia/hypercarbia, and they lack behavioral awareness of hypoxemia/hypercarbia. Optimal oxygenation and ventilation can then be maintained using a mechanical ventilator with mask initially then, if necessary, by tracheostomy to secure the airway and optimize ventilation. This should be accompanied by highly trained home nursing and continuous

monitoring with oximetry and capnography during sleep, with spot checks during wakefulness. The goal should be to maintain hemoglobin saturation values of ≥95% and end-tidal CO₂ values of 35–45 mm Hg, with vigilant evaluation for awake hypoventilation necessitating artificial ventilation up to 24 hours a day as necessary.

Given that the ROHHAD phenotype evolves with advancing age, ongoing care requires regularly scheduled evaluation of all the systems involved to identify and treat further symptoms as they appear. Comprehensive evaluation should ideally occur at a Center of Excellence for ROHHAD and should include respiratory physiology assessment both asleep and awake (in varied levels of age-appropriate exertion, concentrational tasks, quiet play, and eating), screening of chest and abdomen for neural crest tumors in the adrenals or along the sympathetic chain, evaluation of the hypothalamic-pituitary axis with hormonal replacement as necessary, age-appropriate noninvasive evaluation of ANS dysregulation, comprehensive cardiac evaluation for sequelae of recurrent hypoxemia and/or bradycardia, and neurocognitive testing. These evaluations should initially occur at 2- to 3-month intervals, but this schedule may be altered with advancing age, depending on each patient’s clinical condition.

With proper and meticulous management, the ROHHAD phenotype has been observed to “refold,” with the possibility of achieving weight control, eventually recovering spontaneous awake breathing, and improvement of other autonomic measures. Without proper management, oxygen deprivation can lead to irreversible deterioration in patients. However, with prompt diagnosis and aggressive management, including careful attention to the child’s airway, breathing, and circulation, complications can be minimized and the prognosis can be quite favorable, although long-term outcome remains the focus of an international registry (<https://clinicaltrials.gov/show/NCT03135730>).

Paraneoplastic/Autoimmune Hypothesis

Paraneoplastic syndromes are rare disorders caused by a neoplasm triggering an altered immune response that aberrantly attacks and destroys neurons, leading to the nervous system symptoms. An autoimmune or paraneoplastic basis for ROHHAD has been suggested based on neural crest tumors occurring in 40% of ROHHAD patients and reports of encephalitis seen on autopsy. The evidence so far is conflicting, with some reports supporting the autoimmune hypothesis, whereas others do not. Further, the onset of ROHHAD symptoms often precedes identification of a neural crest tumor in ROHHAD patients, and in many cases, neural crest tumors have not been discovered with MRI or even an autopsy. Of note, with excision of the identified neural crest tumor there has not been consistent “recovery” from ROHHAD. Rather, the ROHHAD phenotype continues to “unfold.”

DIFFERENTIAL DIAGNOSIS

Congenital central hypoventilation syndrome is a rare pediatric disorder of the ANS and respiratory control. CCHS is caused by pathogenic variants in the *PHOX2B* gene, which plays an important role in the differentiation and development of the ANS from neural crest progenitor cells (see Chapter 468.2). The hallmark feature of CCHS is life-threatening hypoventilation while sleeping (and, in some cases, also while awake). CCHS patients require artificial ventilatory life support, typically by tracheostomy and mechanical ventilator. Unlike ROHHAD, however, CCHS usually presents in the newborn period, although later-onset CCHS has been diagnosed after 1 month of age, in later childhood, in adolescence, and even in adulthood. CCHS also presents with other symptoms of ANS dysregulation, including altered heart rate regulation, vasomotor tone, and temperature regulation, ophthalmologic manifestations, and reduced gastrointestinal motility. However, CCHS patients are not obese and only rarely have isolated measures of HD. When hypoventilation is observed, a simple blood test can confirm a CCHS diagnosis by looking for pathogenic *PHOX2B* variants.

Prader-Willi syndrome (PWS) shares childhood obesity as one of the most prominent features with ROHHAD. PWS is caused by chromosomal abnormalities at chromosome 15q11-q13, specifically by a lack of the paternal contribution at this region (from genomic deletion, uniparental disomy, or imprinting error), whereas methylation differences, loss of heterozygosity, and pathogenic variants in this region

have been ruled out in a ROHHAD cohort. Infants with PWS present with neonatal hypotonia and failure to thrive (malnutrition). Later, children with PWS develop extreme hyperphagia and obesity. Other major symptoms of PWS include intellectual impairment, maladaptive behaviors, short stature caused by GH insufficiency, hypogonadism, and SDB. In addition, many PWS patients show signs of ANS dysregulation, including altered temperature perception and regulation, strabismus, and high pain threshold.

ROHHAD should also be distinguished from other **obesity-related genetic disorders**. Smith-Magenis syndrome, Carpenter syndrome, and 16p11.2 deletion syndrome present with obesity. However, all of them are additionally marked by early developmental delay, unlike ROHHAD, which has normal neurodevelopment in the absence of cardiorespiratory arrest. Therefore testing for genetic causes of obesity should be undertaken in obese children whose phenotype does not appear to match that of ROHHAD.

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468.4 Long-Term Ventilation and Technology Support: Indications, Principles, Decision-Making, Pragmatics, and Home Provision

Robert J. Graham

INDICATIONS, GOALS, AND DECISION-MAKING

The decision to implement LMV has many challenges from a diversity of underlying pathophysiology, uncertain disease trajectories, the development of new condition-specific therapies, personal experiences, and values held by providers, patients, parents, and the broader community, variability in resources, and lack of standards. Although optimizing gas exchange (i.e., oxygenation and CO₂ removal), mitigating the impact of intercurrent respiratory infections, and supporting neuromuscular-skeletal limitations, growth, and development remain among the primary objectives, LMV represents a tool for the comprehensive care of children with complex needs.

LMV has a role within the broad spectrum of palliative care. It is used proactively to attenuate cumulative morbidities (respiratory and cardiac) associated with progressive neuromuscular conditions, such as Duchenne muscular dystrophy. LMV is also used reactively when acute illness (e.g., acute respiratory distress syndrome or an acute flaccid myelitis) does not resolve. In infants with premature lung disease or complex airway anomalies, LMV may be implemented as a temporary measure, as these conditions may improve with maturity or surgical interventions. LMV can also represent a bridge to lung transplant for those with intrinsic pulmonary or pulmonary vascular disease. More commonly, LMV has become a destination therapy to optimize symptom management and prolong life in complex conditions. Etiologies of the chronic respiratory failure include but are not limited to congenital anomalies (e.g., complex cardiac conditions, central nervous system disorders, interruptions in aerodigestive morphogenesis, and skeletal dysplasias), acquired central neurologic injuries from perinatal, infectious, traumatic, and hypoxic-ischemic events, metabolic disorders, or progressive neuromuscular conditions. Progress in other areas of medicine, such as gene-targeted therapy in spinal muscular atrophy and myotubular myopathy, may alter the LMV decision-making landscape as families foresee the prospect of improvement.

NONINVASIVE AND TRANSTRACHEAL SUPPORTS

The essential modalities for LMV include negative pressure, noninvasive positive pressure ventilation (NIPPV with either continuous or biphasic support provided through an occlusive mask interface), or transtracheal positive pressure. Considerations for a given child or young adult should include but are not limited to anatomic factors, physiologic goals, long-term care goals, comfort, tolerability/

compliance, and safety (mobility/portability, monitoring, device availability and backup, training capacity).

Negative pressure devices, such as the cuirass ventilator, do not require any interface with the face or trachea and are more *natural* from a mechanical perspective. The need for oxygen supplementation is not addressed directly through such a device. NIPPV can address dynamic upper airway obstruction and can augment respiratory mechanics and gas exchange. This modality may, however, have limitations if upper airway obstruction is severe or fixed or the need for oxygen supplementation is high. Masks, prongs, and pillows of varying sizes are available for nasal, oral, combination, and full interface, including those for infants. A mouthpiece interface has also been demonstrated to be effective and feasible. The choice of continuous positive airway pressure (CPAP) versus biphasic positive airway pressure (BiPAP) is dependent on the underlying pathophysiology. Conceptually, CPAP can overcome a dynamic upper airway obstruction and allow for spontaneous ventilation, while BiPAP is more versatile in compensating for upper airway obstruction and supporting lung recruitment and gas exchange. CPAP is limited to management of mild OSA. In addition, BiPAP may allow for home escalation for the management of intercurrent illness with oversight of the medical team. Although NIPPV can be maintained 24 hours a day, efficacy of ventilation, difficult airway considerations (i.e., whether the child can anatomically be intubated), developmental needs, implications for midface hypoplasia, and secretion clearance are among factors that affect the decision to pursue tracheostomy placement and invasive LMV.

Transtracheal LMV provides the most secure and effective respiratory support. Fixed and dynamic upper airway obstruction is bypassed with tracheostomy tube placement. Secretions are more readily cleared from the lower airway. Positive pressure and oxygen delivery via a tracheostomy tube more consistently address primary impairments in gas exchange (within limits) as well as mechanical disadvantages from neuromuscular insufficiency and restrictive disease. When possible, placement of a tracheostomy tube in a child should be coordinated at an institution with pediatric expertise, including in long-term tracheostomy care, because the short-term morbidities and, potentially, mortality are not insignificant.

Individuals using NIPPV are at risk for pressure ulcerations on the face and on the scalp. Proper fit of the interface must be assured because a tighter fit is not necessarily commensurate with better support. Alternating masks on a regular basis may alleviate pressure on a given site. Additional nonadhesive dressings can also be used to facilitate the mask seal and minimize skin breakdown. For those with a tracheostomy tube in place, care of tracheostomy ties and regular assessment of the stoma are required. Moisture-wicking dressings can attenuate risk of maceration, but their use should be balanced against the value of exposure to air for drying. Stomal assessment should include evaluation for granulation, fissures, and traction created by additional torque from ventilator tubing, which should be maintained midline and without weight displacement on the tracheostomy tube itself. Any areas of integument interruption are potential niduses for infection and of great concern for immunocompromised hosts.

AUGMENTED SECRETION CLEARANCE

See Chapter 468.1.

AERODIGESTIVE AND COMMUNICATION CONSIDERATIONS

Assessment of swallowing and speaking capacity should be part of an assessment for LMV and may help guide the modality. Implementation of noninvasive or transtracheal supports will not further impair either of these functions. Rather, the underlying condition is the primary determinant. This consideration is most notable in children or young adults with neurologic injury or neuromuscular conditions. Decision-making around placement of a transabdominal gastric or gastrojejunral enteral feeding tube, if not already in place, should coincide with decisions around LMV. Nasogastric tubes, it should be appreciated, may impair the NIPPV mask seal and cause laryngeal irritation in the long term. Antireflux surgery (i.e., fundoplication) should also be discussed

at this time as providers consider ongoing implications of esophageal reflux, aerophagia, and challenges maintaining jejunostomy tubes.

Use of NIPPV must be approached cautiously in those with impaired swallowing, as positive pressure will increase the risk of macroaspiration and microaspiration. Individuals using NIPPV can eat and drink while on support with risk versus benefit determination and assessment of impact on quality of life. Aerophagia on NIPPV is also problematic, regardless of bulbar function and swallowing capacity; abdominal distention is uncomfortable, contributes to satiety and vomiting risk, and further impairs respiratory mechanics with decreased functional residual capacity and increased inspiratory workload. If a gastrostomy is present, active evacuation of swallowed air and use of passive *venting* tubes can be helpful.

Children with swallowing capacity can continue to eat and drink by mouth with a tracheostomy tube in place on LMV. The presence of a cuffed tracheostomy tube does not prevent aspiration if swallowing is impaired. Speaking may be facilitated by LMV, as settings can be increased or a speaking valve used to increased airflow across the vocal cords. Regardless, multidisciplinary care with a speech-language pathologist, feeding specialist, and augmented communication services can be helpful for many children and their families using LMV. Conditioned aversions to oral stimulation can be challenging for infants, but developmental gains should not be impeded by LMV.

GAS EXCHANGE AND VENTILATOR STRATEGIES

Pressure- or volume-regulated modes, spontaneous or controlled settings, and mixed modes are all feasible for NIPPV and transtracheal supports with new devices. The appropriate support should coincide with oxygenation and ventilation goals on a case-by-case basis. Consideration, however, should be given to the site of care and contingencies for presentation to acute care during intercurrent illness or emergency. Providers should assess limitations in oxygen supplementation outside of the hospital; measured or estimated delivered fractional inspired oxygen (FIO_2) will inform families and providers of capacity when adding oxygen in liters/minute flow to the ventilator circuit; dilution can have a dramatic effect, and achieving $\text{FIO}_2 > 0.60$ may be difficult when oxygen is added to a home ventilator circuit. Safety allowances should also account for the duration of portable oxygen provision, which is based upon liter flow and tank/reservoir volume.

Monitoring of CO_2 in the homecare setting is not usual, although portable end-tidal CO_2 devices are available. Conditions such as CCHS warrant vigilance, and parameters for implementation, or titration, of mechanical ventilation should be discussed with families. Recognition that significant and indolent hypercapnia can precede hypoxia is necessary, and long-term effects on cerebral and pulmonary vasculature should be considered. In the absence of direct CO_2 monitoring, periodic measurement of serum bicarbonate may be helpful to assess for renal compensation for altered CO_2 clearance; however, interpretation may be altered in the presence of diuretic therapy, metabolic disease, or ketogenic diets.

CARDIOPULMONARY INTERACTIONS

Closely linked to the gas-exchange goals are considerations for cardiopulmonary interactions. Although there are subtle implications for systemic venous return of any form of positive pressure ventilation, LMV can be used to decrease transmural myocardial load and to optimize right ventricular afterload through lung recruitment and pulmonary vascular reactivity. The prolonged survival of young males with Duchenne muscular dystrophy is in part the result of consistent respiratory support to optimize lung health and to attenuate myocardial dysfunction. Primary or secondary pulmonary hypertension, whether overt or indolent, requires consideration of oxygenation and ventilation goals. Echocardiograms are not required for all children or young adults with LMV, but this modality may be helpful to guide management in cohorts with congenital heart lesions, cardiomyopathies, severe obstructive pulmonary disease, significant central dysregulation, and on a case-by-case basis.

When considering gas-exchange goals and cardiopulmonary interactions, providers must also consider daytime and nocturnal differences. Neuromuscular-derived hypoventilation is more prominent at

night, as is upper airway obstructive disease; the latter is more important for those using noninvasive LMV. Daytime support provision must account for increased oxygen consumption and demand based on variable activity and stressors, including environmental temperature. Providers and families must factor in mobility, behavioral tolerance, and quality of life.

CHEST WALL/THORACIC CONFIGURATION

Positive pressure through LMV in early childhood for children with neuromuscular conditions and/or restrictive lung disease is also used to improve thoracic compliance and configuration. Lung inflation can be used to attenuate the impact of thoracic asphyxiation as well as progressive parasol chest deformation in diaphragm-dependent conditions, such as spinal muscular atrophy. This use has implications for atelectasis and secretion inspissation, associated pulmonary vasoconstriction, and cumulative restrictive or asymmetric pulmonary mechanics.

NUTRITION AND WEIGHT GAIN

See Chapter 468.1.

DEVELOPMENTAL CONSIDERATIONS

Decisions regarding the LMV modality, noninvasive or transtracheal, requires consideration of development as well. Beyond safety factors, tolerance of interventions, availability of appropriate-sized interfaces, and portability, there remains substantial subjectivity with respect to perspective on the implication for social interactions (i.e., devices covering the face versus a device in the neck). Although there are no published series, long-term or near-continuous NIV also has implications for midface hypoplasia and potentially compounds upper airway obstructive symptoms, as is evident by images of *BiPAP faces*. Swallowing and speech capacity primarily reflect the child's underlying condition and conditioned aversions rather than the LMV itself.

PROJECTED INTERVENTIONS AND NEEDS

The trajectory and management of the underlying disease, as well as symptom management, are the primary drivers in determining the need and duration of LMV. Stakeholders should also consider future interventions, specifically surgical procedures. LMV, noninvasive or transtracheal, can be used to optimize perioperative standing and facilitate recovery and provision of opiate-based analgesia that could alter respiratory drive. The maintenance of a tracheostomy tube in anticipation of sequential surgeries (e.g., spinal instrumentation, craniofacial and airway reconstruction, or serial cardiac interventions) may be required for practical reasons but also minimizes the need for repeated intubation.

PREPARING FOR THE LIVED EXPERIENCE OF LMV AND OTHER TECHNOLOGY SUPPORTS

Emotional challenges are associated with the integration of technology supports into "routine" care and assuming an altered role as a parent and care provider. Addressing practical needs, however, can help attenuate some of the anxiety and allow families to focus on, or revisit, the global goals of care, quality of life, and the role of technology. The family will need to consider each of the following implications.

Financial (e.g., insurance, subsidies, alternative funding, and parental employment): Independent of personal resources, the majority of families with children requiring technology assistance report some degree of financial burden. These costs arise from the direct outlay for equipment and medications, lost work time or need to discontinue/change vocations, home adaptations, and other indirect costs. Accessing a financial counselor or case manager may help identify and navigate through local, state/regional, and government/federal resources. Additional considerations should also be paid to personal trusts, wills, and estate planning, as all of these have implications for long-term benefits and financial supports for the individual with special healthcare needs.

Equipment and supplies: Ideally, the equipment intended for use at home will be tested before discharge to home. Testing ensures proper function and any tolerance. Electrical compatibility with the home

service should be confirmed. Delivery of backup devices (e.g., tracheostomy tubes, including a smaller size for contingency planning; batteries for ventilators; and portable oxygen tanks as a supplement to electric oxygen concentrators) and emergency supplies (e.g., self-inflating respiratory bags, epinephrine for those who have allergy histories, or prophylactic antiepileptic medication for those prone to breakthrough seizures) should be confirmed. Medication supplies and refills should be sufficient to allow for the scheduling of follow-up visits. Providers responsible for recertification or reordering should be identified.

Training: Standards for training and demonstration of competency vary among institutions and across providers. Families and their medical teams should come to an agreement on minimum safety preparation and the number of responsible parties available to assist in the home. Hospital-based training around ventilator use and troubleshooting, central-line care, tracheostomy tube exchanges and suctioning, wound care, and other interventions could include basic life support classes and one-on-one sessions with nurses, respiratory therapists, or other staff, with hands-on or mannequin simulation. Assumption of full care by families while in the hospital can be informative for all stakeholders and reassuring to families; supported replication of the demands of homecare before discharge is ideal.

Augmented staff: Home nursing, hospice, personal care assistants, extended family, and friends represent additional resources for the child and their family. Allowances vary based on the child's age, independence, medical condition, technology dependence, goals of care, and other factors. These individuals may require additional training, but augmenting numbers of proficient homecare providers is crucial for safety and consistency of care. When considering homecare provision, families should consider the type of personnel and how additional supports would allow the child to attend school, the parent to work or maintain the household, continue care when the parent is sick or incapacitated, or assist with other children. The challenges of establishing, training, and maintaining a home staff require time and tolerance, recognizing that the child's safety is the priority.

Monitoring: Conceptually, monitoring is used to detect early physiologic changes, determine adequacy of LMV, and minimize cumulative morbidities or risk of mortality. Continuous direct observation is not practical, or often desirable, in the community setting. Recommendations for monitoring children and young adults on LMV vary based on underlying vulnerability, care setting, activity (e.g., home, long-term care facility, school, or in transport via car), and adjuvant supports (e.g., home nursing or personal care assistant). Pulse oximetry can be used intermittently or on a continuous basis, with oxygen and heart rate parameters determined on a case-by-case basis. Typically, capnography is not available except in cases of central hypoventilation syndromes but can complement oximetry. Internal ventilator alarm settings for both NIPPV and transtracheal ventilators are used to monitor high- and low-pressure parameters and minute ventilation. Stakeholders must acknowledge, however, that internal alarms may be insufficient in the setting of a large mask or peritracheal leak or in the event of a device malfunction.

The child's individual risks and the environmental circumstances drive the balance of extrinsic monitoring (e.g., pulse oximetry and heart rate) and intrinsic device alarms. There are also pragmatic considerations of signal-to-noise when determining monitoring parameters; recurrent false alarms will desensitize providers and may disturb a child's sleep; conversely, wide alarm parameters circumvent early warning systems with significant consequences. Alarm fatigue, as experienced by hospital-based providers, should be discussed, as it can be of great consequence where the resources are not as robust. Simple audio and video monitors (i.e., video cameras) can be used to augment surveillance and may help families in their activities of daily living.

Adaptations to the homecare setting: Modifications to the home may be required to ease care and optimize safety. Ramps for wheelchair access will permit ingress and egress. Lift systems can minimize physical burden and injury risk to providers. Doorways can be expanded to permit access to multiple rooms. Alternative bath and toileting accommodations may be needed. Electrical system upgrades with grounding

and increased amperage are often required for equipment demand and safety.

Transportation: Discharge planning for a child or young adult with technology dependence should include transportation to school, community programs, routine family activities, and scheduled or urgent medical services. Proximity (rural or urban), the child's mobility, weather, and the need for monitoring en route are other considerations. Adaptive car seats or car beds can be purchased. Personal vehicles may need expensive modifications, including lifts and power inverters. Allowances may also be required for one person to drive while another (i.e., nurse, parent, or care assistant) tends to the child. If traveling long distances, perhaps on vacation, advanced planning might include identification of hospitals along the route and reciprocal equipment companies to assist with unexpected supply needs.

Air transportation: If a family anticipates travel by plane, contingencies should be made for oxygen support at altitude, recognizing that most commercial airlines pressurize their cabins to the equivalent of 7,000–8,000 feet. Portable oxygen sources may have less liter flow capacity than stationary or home devices; there is also a need to differentiate continuous versus on-demand flow options. Space and limited supplies inflight should be considerations. Power wheelchairs are prone to damage when placed in cargo holds, and ground crews likely require explicit instructions. Providers may need to write letters for airport security and airlines for excess baggage, electronic equipment, medication, and fluid allowance. Families can also consider sending additional supplies to the final destination in advance.

Environmental stressors: Extreme temperatures, heat or cold, variability in humidity, and other environmental variables can greatly affect the well-being of a child with underlying cardiorespiratory insufficiency or other special healthcare needs. Home adaptations to permit climate control for the child's room may be required. Families may consider prewarming, or cooling, vehicles for routine excursions, and limitations on day-to-day activities are warranted at times. Augmented hydration needs should be reviewed with medical providers, along with routine sunscreen and preventive measures.

Preparation for transition to the homecare setting may include a period of quiescence, depending on the circumstances and family preferences. Establishing a period of stability, when there has been no need to alter supports, may minimize unplanned readmissions.

Community Resources

The transition from the acute care or rehabilitation facility to home-care setting is often much anticipated and welcomed. This step can also be frightening and overwhelming, whether it represents the first time home or a return after an acute illness or planned surgery. Hospital-based providers can partner with families to alleviate some anxiety and to avoid potential pitfalls through proactive engagement. Hand-off to outpatient and community stakeholders can include the following:

The community medical practice: Updates on problem lists, projected follow-up, medication and equipment needs, routine health maintenance and preventive measures (e.g., immunizations), special considerations for nutrition, identification of specialty providers and follow-up schedules, and case-specific risks.

First responders: Confirmation that the family has the capacity to call emergency services, outreach to police and ambulance services to outline baseline needs, special condition-specific interventions or precautions, identification of equipment that may need to be taken with the child in the event of an emergency, determination of emergency destination (i.e., local hospital or referral center), and clarification of resuscitation status and life-sustaining therapies.

Therapy programs: Physical, occupational, speech-language/feeding, and other therapists benefit from hospital-based assessments and outlines of expectations, restrictions, and uncertainties.

Educational programs/schools/day habilitation: Integration into community services requires evaluation of developmental needs and potential adaptive settings, equipment, services, staffing, and transportation for all ages.

Power and water: Alerting local housing, social, power, and water authorities to medical necessities can facilitate prioritization of service

restoration during natural disasters or other interruptions and identify programs to defray incurred costs with increased technology-driven electrical usage (e.g., home ventilators, oxygen concentrators, and climate control).

Families may find additional resources through faith-based institutions, nonprofit and advocacy groups (e.g., Kiwanis, Shriners, Boy Scouts), and condition-specific entities, such as the Muscular Dystrophy Association. Outreach to other families with similar circumstances can also be helpful with the caveat that their recommendations reflect their own goals and lived experience with special healthcare needs.

Subacute Care

Local resources for medical services should be identified in advance. This begins with the primary care and first responders but extends to local and regional hospitals. It is important to determine the range of services available and to identify specific providers who would familiarize themselves with a given case. The child with technology dependence will experience intercurrent illnesses or unexpected accidents that require evaluation, but may not always necessitate transport to tertiary care or referral centers. Individual care plans can be developed in conjunction with the family and local providers and may include thresholds for transfer.

Families should also consider bringing home equipment and supplies when presenting to urgent and acute care settings. Devices such as pediatric NIPPV masks and cough-assist machines or compounded medications may not be available at every facility. Short-term evaluations may become protracted, and lack of routine care provision may compound the immediate issues.

Emergency and Acute Care

Providers and families should acknowledge that children with special healthcare needs (CSHCN) and LMV are at risk for repeated hospitalization. Progression of underlying illnesses (e.g., heart failure), planned surgical interventions (e.g., spinal instrumentation, bronchoscopy surveillance, tendon releases), or superimposed acute illnesses (e.g., pneumonia, gastroenteritis, appendicitis, recurrent seizures) may necessitate readmission. Those children who are technology dependent have a higher likelihood of requiring critical care services because of the nature of their needs and their vulnerability. Preventable equipment-related issues may be obviated through the planning described previously. Once hospitalized, CSHCN are at greater risk of medical error and incur more interventions when compared with otherwise healthy children. Parents should be encouraged to develop a medical passport and reference list of providers to facilitate communication and consistency of care. Referencing established care guidelines and, again, developing individualized care plans may be helpful.

Quality of Life

CSHCN of increasing complexity and technology dependence are thriving in the homecare setting as a result of advances in medical care, shared decision-making, community services, and most notably, extensive, vigilant, and proactive care efforts by their families. Adaptations allow for participation in all aspects of family, school, and community activities. Although individual trajectory and subsequent needs may be difficult to predict, all stakeholders should acknowledge the impact of chronic care on the family unit and health-related quality of life. The evolution of a medical home for this cohort of children will require provisions for family mental health, sibling supports, respite, and other measures to optimize outcomes.

TRANSITIONING FROM ACUTE CARE TO REHABILITATION OR COMMUNITY SETTING

Disposition of children and young adults with LMV will vary based on their relative stability, local support services, and goals of care. A proactive, flexible, comprehensive care model is required to assure safe and effective provision. The impacts of care needs on the child and family are inextricably linked.

ROUTINE HEALTH MAINTENANCE

Airway Evaluation

There is no standard for regular airway assessment for children with LMV, specifically those with transtracheal support, but annual evaluation should represent the minimum. Office-based transtracheal tube endoscopy can facilitate assessment of tube upsizing for linear growth, presence of granulation tissue, airway inflammation, and general mucosal integrity. Formal diagnostic laryngoscopy and bronchoscopy under general anesthesia are required to assess for suprastomal and laryngeal-level pathology along with the rare acquired tracheoesophageal fistulae. Independent of routine evaluation, recurrent or unexpected tracheal bleeding may warrant evaluation for a tracheal-vascular fistula via CT angiogram and bronchoscopy.

Bacterial Colonization

Chronic respiratory failure lends itself to airway bacterial colonization because of alterations in secretion clearance, aerodigestive interactions, the presence of artificial airways with the development of biofilms, and other factors. Hydrophilic and gram-negative bacteria (e.g., *Pseudomonas*, *Serratia*, and *Stenotrophomonas*) are common. There is no standard of care for determining pathogenicity versus colonization. Use of systemic or inhaled antibacterial agents to decrease colonization load, frequency of tracheostomy tube exchanges to reduce biofilm accumulation, utility of viral screening, and threshold for treatment of an acute lower airway process or tracheitis is provider and case dependent. Providers should appreciate that recurrent empiric antibacterial treatment may select for resistant bacterial strains and has implications for enteric bacterial colonization.

Dental Care

Routine daily and office-based dental care should follow standard recommendations for all children. Extrapolation from the acute care setting and general population would suggest that oropharyngeal care and minimization of bacterial overgrowth would affect the risk of superimposed respiratory illness in LMV and long-term cardiovascular outcomes, respectively. Special consideration with respect to aspiration risk, developmental tolerance, and prophylaxis and procedural sedation for intervention may require engagement of specialty providers.

Immunizations

No immunizations are specifically indicated for individuals receiving LMV. Routine provision is recommended, including seasonal vaccinations for viral pathogens. Expansion of exposure precautions, as experienced during the COVID-19 pandemic, also remain essential.

Radiography, Laboratory, Polysomnography, and Pulmonary Function Testing

There are no recommendations for routine chest radiography, standard or cross-sectional, in the context of LMV. The cumulative radiation exposure would need to be considered. Gas exchange adequacy can often be assessed noninvasively. Venous, capillary, or arterial puncture for determining resting and long-term oxygenation and ventilation status may be of limited utility and validity, as intercurrent illness, technique with tourniquet, and associated agitation will alter results. Condition-specific (e.g., muscular dystrophy) recommendations for polysomnography, spirometry, or pulmonary function testing have been established and may be extrapolated with some validity. Regular assessment may also be helpful when gauging disease trajectory, LMV titration, safety parameters, and weaning potential.

LONG-TERM MECHANICAL VENTILATION WEANING AND TRACHEAL DECANNULATION

Reassessment of the role of LMV should be part of routine and family-centered care. Determination should include but is not limited to the factors described earlier with open discussion of goals of care, developmental appropriateness, physiologic and anatomic consideration, growth implications, new treatments, and contingencies. As there are currently no definitive conditioning regimens or LMV

weaning strategies, providers can determine the value of time off versus decreased level of supports as well as pragmatic considerations for the child and family. Continuity of care, however, holds implicit value. Monitoring provision may need to be increased during weaning.

If tracheal decannulation is required, a formal diagnostic laryngoscopy and bronchoscopy should be considered to rule out granulation (suprastomal and infrastomal) and dynamic airway collapse that may prohibit immediate tracheostomy tube removal. If positive pressure or oxygen supplementation will still be required after decannulation, determination of the child's tolerance of noninvasive ventilation or other interventions (e.g., cough assist) should be determined in advance. Desensitization may be required.

Ultimately, LMV has an increasing role in the support of children and young adults with chronic respiratory failure. Decision-making about any technology supports can be challenging from an emotional, practical, and ethical perspective. As families and other stakeholders explore options, the goal at these consequential junctures should be to align expectations, hopes, and potential lived experiences. Everyone should acknowledge the uncertainties and the potential to withhold, withdraw, and regularly reassess, even in the community setting. As this population of CSHCN and technology dependence ages, transition from pediatric to adult services should also be anticipated.

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