Chapter 391

Wheezing, Bronchiolitis, and Bronchitis

391.1 Wheezing in Infants: Bronchiolitis

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DEFINITIONS AND GENERAL PATHOPHYSIOLOGY

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

Infants are more likely to wheeze than older children and adults as a result of a differing set of lung mechanics. The obstruction to flow is affected by the airway caliber and compliance of the infant lung. Resistance to airflow through a tube is inversely related to the radius of the tube to the 4th power. In children younger than 5 yr old, small-caliber

peripheral airways can contribute up to 50% of the total airway resistance. Marginal additional narrowing can cause further flow limitation and a subsequent wheeze.

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

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

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

ETIOLOGY

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

Acute Bronchiolitis and Inflammation of the Airway

Infection can cause obstruction to flow by internal narrowing of the airways.

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

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

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

Not all infected infants develop lower respiratory tract illness. Host anatomic and immunologic factors play a significant role in the severity of the clinical syndrome, as does the nature of the viral pathogen.

Table 391-1 Differential Diagnosis of Wheezing in Infancy

INFECTION
Viral
Respiratory syncytial virus
Human metapneumovirus
Parainfluenza
Adenovirus
Influenza
Rhinovirus
Bocavirus
Coronavirus
Enterovirus
Other
Chlamydia trachomatis
Tuberculosis
Histoplasmosis
Papillomatosis
ASTHMA
Transient wheezer (resolved by 6 yr of age)
• Initial risk factor is primarily diminished lung size
Persistent wheezers (persists beyond 6 yr of age)
• Initial risk factors include parental asthma history, atopic dermatitis, allergen sensitization, peripheral eosinophilia (>4%) and wheezing unrelated to colds in the 1st yr of life
• At increased risk of developing clinical asthma
Late-onset wheezer (symptoms begin after age 3 yr and persist)
ANATOMIC ABNORMALITIES
Central Airway Abnormalities
Malacia of the larynx, trachea, and/or bronchi
Laryngeal or tracheal web
Tracheoesophageal fistula (specifically H-type fistula)
Laryngeal cleft (resulting in aspiration)
Extrinsic Airway Anomalies Resulting in Airway Compression
Vascular ring or sling
Mediastinal lymphadenopathy from infection or tumor
Mediastinal mass or tumor
Esophageal foreign body
Intrinsic Airway Anomalies
Airway hemangioma, other tumor
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
Immunodeficiency States
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
Interstitial lung disease, including bronchiolitis obliterans
Heart failure
Anaphylaxis
Inhalation injury—burns

Infants with preexistent smaller airways and diminished lung function have a more severe course. In addition, RSV infection incites a complex immune response. Eosinophils degranulate and release eosinophil cationic protein, which is cytotoxic to airway epithelium. Innate immunity plays a significant role and can depend on polymorphisms in toll-like receptors, interferons, interleukins, and nuclear factor κB. Chemokines and cytokines, such as tumor necrosis factor α, may be differentially expressed, depending on the inciting virus. Coinfection with more than 1 virus can also alter the clinical manifestations and/or severity of presentation.

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

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

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

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

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

Other Causes

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

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

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

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

CLINICAL MANIFESTATIONS

History and Physical Examination

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

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

Table 391-2 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?
Change in caregivers or chance of nonaccidental trauma?

Wheezing produces an expiratory whistling sound that can be polyphonic or monophonic. Expiratory time may be prolonged. Biphasic wheezing can occur if there is a central, large airway obstruction. The degree of tachypnea does not always correlate with the degree of hypoxemia or hypercarbia, so pulse oximetry and noninvasive determination of carbon dioxide is essential. Work of breathing may be markedly increased, with nasal flaring and retractions. *Complete obstruction to airflow can eliminate the turbulence that causes wheezing; thus the lack of audible wheezing is not reassuring if the infant shows other signs of respiratory distress.* Barely audible breath sounds suggest very severe disease with nearly complete bronchiolar obstruction.

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

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

Diagnostic Evaluation

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

The diagnosis of **acute bronchiolitis** is clinical, particularly in a previously healthy infant presenting with a 1st-time wheezing episode during a community outbreak. Chest radiography can reveal hyperinflated lungs with patchy atelectasis but is not indicated in all patients with bronchiolitis. The white blood cell and differential counts are usually normal. Viral testing (polymerase chain reaction, rapid immunofluorescence, or viral culture) is helpful if the diagnosis is uncertain or for epidemiologic purposes but is not indicated in uncomplicated bronchiolitis. Because concurrent bacterial infection (sepsis, pneumonia, meningitis) is highly unlikely, confirmation of viral bronchiolitis may obviate the need for a sepsis evaluation in the febrile infant older than 28 days and assist with respiratory precautions and isolation if the patient requires hospitalization.

Treatment

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

The use of ipratropium bromide in this population is controversial, but it appears to be somewhat effective as an adjunct therapy. It is also useful in infants with significant tracheal and bronchial malacia who may be made worse by β_2-agonists such as albuterol because of the subsequent decrease in smooth muscle tone.

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

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

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

A number of agents have been proposed as adjunctive therapies for bronchiolitis. Bronchodilators may produce short-term improvement in clinical features. This must be placed in context of potential adverse effects and the lack of any evidence indicating improvement in overall course of the disease. Systematic reviews and meta-analyses of randomized controlled trials have failed to show a benefit from bronchodilators in uncomplicated bronchiolitis. Corticosteroids, whether parenteral, oral, or inhaled, have been used for bronchiolitis despite conflicting and often negative studies. Corticosteroids are not recommended in previously healthy infants with RSV. Ribavirin, an antiviral agent administered by aerosol, has been used for infants with RSV who have congenital heart disease or chronic lung disease. There is no convincing evidence of a positive impact on clinically important

outcomes such as mortality and duration of hospitalization. Antibiotics have no value unless there is coexisting bacterial infection. Likewise, there is no support for RSV immunoglobulin administration during acute episodes of RSV bronchiolitis in previously healthy children. Combined therapy with nebulized epinephrine and dexamethasone has been used with some success, but additional studies are needed to confirm its efficacy and investigate the long-term adverse effects in infants before this combination can be recommended. Nebulized hypertonic saline has been reported to have some benefit, and may shorten hospital length of stay. One study suggested that on demand therapy with inhaled epinephrine or saline was more effective than scheduled fixed dosing. Heliox delivered by tight fitting mask or by continuous positive airway pressure has been of some benefit in moderately to severely affected patients with bronchiolitis.

Certain (10%) low risk patients with bronchiolitis and an oxygen requirement may be discharged from the emergency department to receive **home oxygen therapy**. Criteria for home oxygen therapy includes: typical clinical features (no apnea, wheezing ± crackles); 2 mo-2 yr of age (>44 wk gestational age); first episode of wheezing; illness during RSV season; secretions managed by parents with bulb suctioning; smoke free home; reliable family with good access to healthcare; altitude ≤6,000 feet; absence of toxic appearance or proven bacterial disease; apparent life-threatening event; cardiac, pulmonary, immunodeficiency, or neuromuscular disorders; baseline oxygen requirement prior to current illness; mild illness as evident by feeding well and alert and active; minimal retractions; respiratory rate <50 breaths/min; oxygenation >90% on ≤0.5 L/min of oxygen. All patients must have follow-up within 24 hr of discharge from the emergency room by their primary care provider or by the emergency room staff. Chest physiotherapy does not improve disease course in hospitalized infants with bronchiolitis who are not mechanically ventilated.

PROGNOSIS

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

PREVENTION

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

Bibliography is available at Expert Consult.

391.2 Bronchitis

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

Acute tracheobronchitis is a term used when the trachea is prominently involved. Nasopharyngitis may also be present, and a variety of viral and bacterial agents, such as those causing influenza, pertussis, and diphtheria, may be responsible. Isolation of common bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae* from the sputum might not imply a bacterial cause that requires antibiotic therapy.

ACUTE BRONCHITIS

Clinical Manifestations

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

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

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

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

Differential Diagnosis

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

Treatment

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

CHRONIC BRONCHITIS

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

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

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Table 391-3 Disorders with Cough as a Prominent Finding

CATEGORY	DIAGNOSES
Inflammatory	Asthma
Chronic pulmonary processes	Bronchopulmonary dysplasia Postinfectious bronchiectasis Cystic fibrosis Tracheomalacia or bronchomalacia Ciliary abnormalities 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 *Chlamydia, Ureaplasma* (infants) *Bordetella pertussis* *Mycoplasma pneumoniae*
Acquired	Foreign-body aspiration, tracheal or esophageal

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 391-3). 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 a chronic (>3 wk) wet cough, characterized by bacterial counts of 10^4 colony-forming units/mL or greater from bronchoalveolar lavage and resolution of cough within 2 wk of treatment with antimicrobial therapy.

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 passive smoke. Marijuana smoke and inhalants are other 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 1 to pulmonary symptoms is difficult to discern.

Bibliography is available at Expert Consult.

391.3 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 an altered state of respiratory epithelial function and is most frequently encountered in the setting of underlying pulmonary or congenital cardiac disease, although there have been reports of plastic bronchitis complicating lymphangitic disorders, pulmonary infections, and the acute chest syndrome of sickle cell disease. In comparison to the smaller bronchial and bronchiolar casts seen with mucus plugging, the lesions of plastic bronchitis are more extensive, with casts that can outline large segments of the airway to the level of the terminal bronchioles (Fig. 391-1). These casts may be spontaneously expectorated or may require bronchoscopic removal for relief of potentially fatal airway obstruction. Cast composition varies, though typically consists of either a fibrin-predominant or mucin-predominant laminated matrix with or without inflammatory cell infiltration. Plastic bronchitis may be classified according to an associated disease, the cast histology, or a combination.

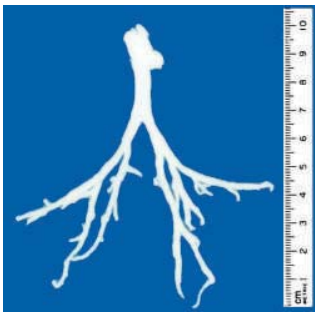

Figure 391-1 Tracheobronchial casts following bronchoscopic extraction. Casts show branched architecture corresponding to the bronchial tree. *(From Hasan RA, Black C, Reddy R: Plastic bronchitis in children.* Fetal Pediatr Pathol *31;87–93, 2012, Fig. 5, p. 91.)*

EPIDEMIOLOGY

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

PATHOGENESIS

The mechanism of cast formation is unclear, although it is believed to vary based on the underlying disease association and cast type. One classification system differentiates type 1 inflammatory casts, composed of primarily of fibrin with neutrophilic and more often eosinophilic infiltration, and type 2 casts, composed primarily of mucin with little to no cellular infiltration. Type 1 casts may be associated with inflammatory and infectious disorders of the lung, while type 2 casts may be associated with structural heart disease. However, these distinctions are not absolute; patients with structural heart disease can have mucin-predominant casts and patients with asthma or atopic disease can have fibrin-predominant casts, with both mucin casts and fibrin casts demonstrating various degrees of cellular infiltration.

Cast formation in the setting of structural heart disease may result from alterations in pulmonary blood flow or from alterations in lymphatic drainage, either congenital or secondary to the protein-losing enteropathy associated with Fontan physiology. Mucin-predominant casts are believed to arise secondary to mucus gland hypersecretion as well as decreased mucociliary clearance.

CLINICAL MANIFESTATIONS

Patients with plastic bronchitis may present with cough, dyspnea, wheeze, or pleuritic chest pain. Depending on the degree of airway obstruction, patients may be hypoxemic or in severe respiratory distress. The expectoration of large, branched casts that are often tan in

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color and rubbery in consistency is pathognomonic for plastic bronchitis. Lung examination may reveal diminished breath sounds or wheezing in the affected area. Rarely, auscultation may reveal a sound similar to a flag flapping in the wind *(bruit de drapeau)*, believed to be related to the free end of a cast striking the bronchial wall during inspiration or expiration. Further examination may provide clues to underlying comorbidities.

DIAGNOSIS

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

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

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

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

TREATMENT

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

COMPLICATIONS AND PROGNOSIS

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

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Chapter 400

Community-Acquired Pneumonia

Matthew S. Kelly and Thomas J. Sandora

EPIDEMIOLOGY

Pneumonia, defined as inflammation of the lung parenchyma, is the leading cause of death globally among children younger than age 5 yr, accounting for an estimated 1.2 million (18% total) deaths annually (Fig. 400-1). The incidence of pneumonia is more than 10-fold higher (0.29 episodes vs 0.03 episodes), and the number of childhood-related deaths from pneumonia ≈2,000 fold higher, in developing than in developed countries (Table 400-1). Fifteen countries account for more than three-fourths of all pediatric deaths from pneumonia.

In the United States from 1939-1996, pneumonia mortality in children declined by 97%; in 1970, pneumonia accounted for 9% of all deaths of children younger than age 5 yr compared to 2% in 2007. It is probable that this decline results from the introduction of antibiotics, vaccines, and the expansion of medical insurance coverage for children. *Haemophilus influenzae* type b (see Chapter 194) was an important cause of bacterial pneumonia in young children but became uncommon with the routine use of effective vaccines, while measles vaccine greatly reduced the incidence of measles-related pneumonia deaths in developing countries. Improved access to healthcare in rural areas of developing countries and the introduction of pneumococcal conjugate vaccines (see Chapter 182) were also important contributors to the further reductions in pneumonia-related deaths achieved over the past decade.

ETIOLOGY

Although most cases of pneumonia are caused by microorganisms, noninfectious causes include aspiration (of food or gastric acid, foreign bodies, hydrocarbons, and lipoid substances), hypersensitivity reactions, and drug- or radiation-induced pneumonitis. The cause of pneumonia in an individual patient is often difficult to determine because direct culture of lung tissue is invasive and rarely performed. Cultures performed on specimens in children obtained from the upper respiratory tract or sputum typically do not accurately reflect the cause of lower respiratory tract infection. With the use of molecular diagnostic testing, a bacterial or viral cause of pneumonia can be identified in

40-80% of children with community-acquired pneumonia. *Streptococcus pneumoniae* (pneumococcus) is the most common bacterial pathogen in children 3 wk to 4 yr of age, whereas *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are the most frequent bacterial pathogens in children age 5 yr and older. In addition to pneumococcus, other bacterial causes of pneumonia in previously healthy children in the United States include group A streptococcus *(Streptococcus pyogenes)* and *Staphylococcus aureus* (see Chapter 181.1 and Table 400-2). *S. aureus* pneumonia often complicates an illness caused by influenza viruses.

S. pneumoniae, H. influenzae, and *S. aureus* are the major causes of hospitalization and death from bacterial pneumonia among children in developing countries, although in children with HIV infection, *Mycobacterium tuberculosis* (see Chapter 215), atypical mycobacteria,

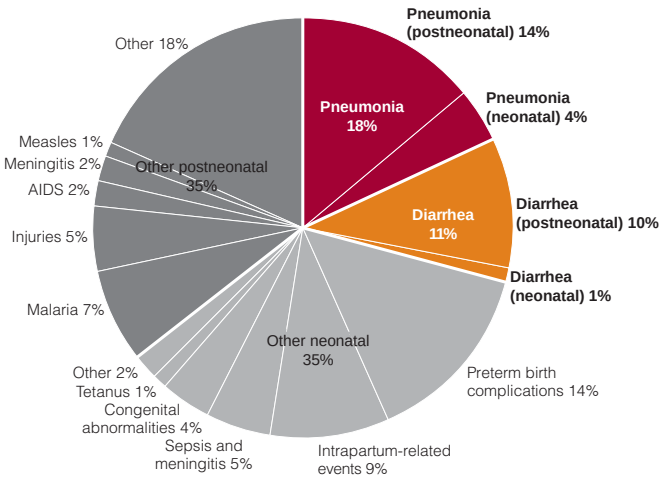

Figure 400-1 Pneumonia is the leading killer of children worldwide, as shown by this illustration of global distribution of cause-specific mortality among children younger than age 5 yr in 2010. Pneumonia causes 18% of all under-5 deaths. Values may not sum to 100% because of rounding. *(From Black RE, Allen LH, Bhutta ZA, et al: Maternal and child undernutrition: global and regional exposures and health consequences.* Lancet *371:243–260, 2008; and Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000.* Lancet *379:2151–2161, 2012, Fig. 2.)*

Salmonella (see Chapter 198), *Escherichia coli* (see Chapter 200), and *Pneumocystis jiroveci* (see Chapter 244) must be considered. The incidence of pneumonia caused by *H. influenzae* or *S. pneumoniae* has been significantly reduced in areas where routine immunization has been implemented.

Viral pathogens are a prominent cause of lower respiratory tract infections in infants and children older than 1 mo but younger than 5 yr of age. Viruses can be detected in 40-80% of children with pneumonia using molecular diagnostic methods. Of the respiratory viruses, respiratory syncytial virus (RSV) (see Chapter 260) and rhinoviruses are the most commonly identified pathogens, especially in children younger than 2 yr of age. However, the role of rhinoviruses in severe lower respiratory tract infection remains poorly defined as these viruses are frequently detected in infections with 2 or more pathogens and among asymptomatic children. Other common viruses causing pneumonia include influenza virus (see Chapter 258), parainfluenza viruses, adenoviruses, enteroviruses, and human metapneumovirus. Infection with more than 1 respiratory virus occurs in up to 20% of cases. The age of the patient may help identify possible pathogens (Table 400-3).

Lower respiratory tract viral infections are much more common in the fall and winter in both the northern and southern hemispheres in relation to the seasonal epidemics of respiratory viral infection that occur each year. The typical pattern of these epidemics usually begins in the fall, when parainfluenza infections appear and most often manifest as croup. Later in winter, RSV, human metapneumovirus, and influenza viruses cause widespread infection, including upper respiratory tract infections, bronchiolitis, and pneumonia. RSV is particularly severe among infants and young children, whereas influenza virus causes disease and excess hospitalization for acute respiratory illness in all age groups. Knowledge of the prevailing viral epidemic may lead to a presumptive initial diagnosis.

Immunization status is relevant because children fully immunized against *H. influenzae* type b and *S. pneumoniae* are less likely to be infected with these pathogens. Children who are immunosuppressed or who have an underlying illness may be at risk for specific pathogens, such as *Pseudomonas* spp. in patients with cystic fibrosis (see Chapter 403).

PATHOGENESIS

The lower respiratory tract is normally kept sterile by physiologic defense mechanisms, including mucociliary clearance, the properties of normal secretions such as secretory immunoglobulin (Ig) A, and

Table 400-1 Incidence of Pneumonia Cases and Pneumonia Deaths Among Children Younger Than Age 5 Yr, by UNICEF Region, 2004*

UNICEF REGIONS	NUMBER OF CHILDREN YOUNGER THAN 5 YR OF AGE (IN THOUSANDS)	NUMBER OF CHILDHOOD PNEUMONIA DEATHS (IN THOUSANDS)	INCIDENCE OF PNEUMONIA CASES (EPISODES PER CHILD PER YEAR)	TOTAL NUMBER OF PNEUMONIA EPISODES (IN THOUSANDS)
South Asia	169,300	702	0.36	61,300
Sub-Saharan Africa	117,300	1,022	0.30	35,200
Middle East and North Africa	43,400	82	0.26	11,300
East Asia and Pacific	146,400	158	0.24	34,500
Latin America and Caribbean	56,500	50	0.22	12,200
Central and Eastern Europe and the Commonwealth of Independent States	26,400	29	0.09	2,400
Developing countries	533,000	2,039	0.29	154,500
Industrialized countries	54,200	1	0.03	1,600
World	**613,600**	**2,044**	**0.26**	**158,500**

*Regional estimates in Columns 2, 3, and 5 do not add up to the world total because of rounding.
From Wardlaw T, Salama P, White Johansson E: Pneumonia: the leading killer of children, Lancet *368:1048–1050, 2006.*

Table 400-2 Causes of Infectious Pneumonia

BACTERIAL	
Common	
Streptococcus pneumoniae	Consolidation, empyema
Group B streptococci	Neonates
Group A streptococci	Empyema
*Mycoplasma pneumoniae**	Adolescents; summer-fall epidemics
*Chlamydophila pneumoniae**	Adolescents
Chlamydia trachomatis	Infants
Mixed anaerobes	Aspiration pneumonia
Gram-negative enterics	Nosocomial pneumonia
Uncommon	
Haemophilus influenzae type b	Unimmunized
Staphylococcus aureus	Pneumatoceles, empyema; infants
Moraxella catarrhalis	
Neisseria meningitidis	
Francisella tularensis	Animal, tick, fly contact; bioterrorism
Nocardia species	Immunosuppressed persons
*Chlamydophila psittaci**	Bird contact (especially parakeets)
Yersinia pestis	Plague; rat contact; bioterrorism
Legionella species*	Exposure to contaminated water; nosocomial
*Coxiella burnetii**	Q fever; animal (goat, sheep, cattle) exposure
VIRAL	
Common	
Respiratory syncytial virus	Bronchiolitis
Parainfluenza types 1-3	Croup
Influenzas A, B	High fever; winter months
Adenovirus	Can be severe; often occurs between January and April
Human metapneumovirus	Similar to respiratory syncytial virus
Uncommon	
Rhinovirus	Rhinorrhea
Enterovirus	Neonates
Herpes simplex	Neonates
Cytomegalovirus	Infants, immunosuppressed persons
Measles	Rash, coryza, conjunctivitis
Varicella	Adolescents or unimmunized
Hantavirus	Southwestern United States, rodents
Coronavirus (severe acute respiratory syndrome, Middle East respiratory syndrome [MERS])	Asia, Arabian peninsula
FUNGAL	
Histoplasma capsulatum	Ohio/Mississippi River valley; bird, bat contact
Blastomyces dermatitidis	Ohio/Mississippi River valley
Coccidioides immitis	Southwest United States
Cryptococcus neoformans	Bird contact
Aspergillus species	Immunosuppressed persons; nodular lung infection
Mucormycosis	Immunosuppressed persons
Pneumocystis jiroveci	Immunosuppressed, steroids
RICKETTSIAL	
Rickettsia rickettsiae	Tick bite
MYCOBACTERIAL	
Mycobacterium tuberculosis	Travel to endemic region; exposure to high-risk persons
Mycobacterium avium complex	Immunosuppressed persons
PARASITIC	
Various parasites (e.g., Ascaris, *Strongyloides* species)	Eosinophilic pneumonia

*Atypical pneumonia syndrome; may have extrapulmonary manifestations, low-grade fever, patchy diffuse infiltrates, poor response to β-lactam antibiotics, and negative sputum Gram stain.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis & therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 29.*

Table 400-3 Etiologic Agents Grouped by Age of the Patient

AGE GROUP	FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)
Neonates (<3 wk)	Group B streptococcus, *Escherichia coli,* other Gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type b,* nontypeable)
3 wk-3 mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypeable); if patient is afebrile, consider *Chlamydia trachomatis*
4 mo-4 yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypeable), *Mycoplasma pneumoniae,* group A streptococcus
≥5 yr	*M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b,* nontypeable), influenza viruses, adenovirus, other respiratory viruses, *Legionella pneumophila*

**H. influenzae* type b is uncommon with routine *H. influenzae* type b immunization.

Adapted from Kliegman RM, Marcdante KJ, Jenson HJ, et al: Nelson essentials of pediatrics, *ed 5, Philadelphia, 2006, Elsevier, p. 504.*

clearing of the airway by coughing. Immunologic defense mechanisms of the lung that limit invasion by pathogenic organisms include macrophages that are present in alveoli and bronchioles, secretory IgA, and other immunoglobulins. Trauma, anesthesia, and aspiration increase the risk of pulmonary infection.

Viral pneumonia usually results from spread of infection along the airways, accompanied by direct injury of the respiratory epithelium, which results in airway obstruction from swelling, abnormal secretions, and cellular debris. The small caliber of airways in young infants makes such patients particularly susceptible to severe infection. Atelectasis, interstitial edema, and ventilation–perfusion mismatch causing significant hypoxemia often accompany airway obstruction. Viral infection of the respiratory tract can also predispose to secondary bacterial infection by disturbing normal host defense mechanisms, altering secretions, and modifying the bacterial flora.

Bacterial pneumonia most often occurs when respiratory tract organisms colonize the trachea and subsequently gain access to the lungs, but pneumonia may also result from direct seeding of lung tissue after bacteremia. When bacterial infection is established in the lung parenchyma, the pathologic process varies according to the invading organism. *M. pneumoniae* (see Chapter 223) attaches to the respiratory epithelium, inhibits ciliary action, and leads to cellular destruction and an inflammatory response in the submucosa. As the infection progresses, sloughed cellular debris, inflammatory cells, and mucus cause airway obstruction, with spread of infection occurring along the bronchial tree, as it does in viral pneumonia.

S. pneumoniae produces local edema that aids in the proliferation of organisms and their spread into adjacent portions of lung, often resulting in the characteristic focal lobar involvement.

Group A streptococcus infection of the lower respiratory tract results in more diffuse infection with interstitial pneumonia. The pathology includes necrosis of tracheobronchial mucosa; formation of large amounts of exudate, edema, and local hemorrhage, with extension into the interalveolar septa; and involvement of lymphatic vessels and the increased likelihood of pleural involvement.

S. aureus pneumonia manifests in confluent bronchopneumonia, which is often unilateral and characterized by the presence of extensive areas of hemorrhagic necrosis and irregular areas of cavitation of the lung parenchyma, resulting in pneumatoceles, empyema, or, at times, bronchopulmonary fistulas.

Table 400-4	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	
Immotile cilia syndrome	
Kartagener syndrome	
ANATOMIC DISORDERS	
Pulmonary sequestration	
Lobar emphysema	
Gastroesophageal reflux	
Foreign body	
Tracheoesophageal fistula (H type)	
Bronchiectasis	
Aspiration (oropharyngeal incoordination)	
Aberrant bronchus	

From Kliegman RM, Marcdante KJ, Jenson HJ, et al: Nelson essentials of pediatrics, *ed 5, Philadelphia, 2006, Elsevier, p. 507.*

Recurrent pneumonia is defined **as 2 or more** episodes in a single year **or 3 or more** episodes ever, with radiographic clearing between occurrences. An underlying disorder should be considered if a child experiences recurrent pneumonia (Table 400-4).

CLINICAL MANIFESTATIONS

Pneumonia is frequently preceded by several days of symptoms of an upper respiratory tract infection, typically rhinitis and cough. In viral pneumonia, fever is usually present but temperatures are generally lower than in bacterial pneumonia. Tachypnea is the most consistent clinical manifestation of pneumonia. Increased work of breathing accompanied by intercostal, subcostal, and suprasternal retractions, nasal flaring, and use of accessory muscles is common. Severe infection may be accompanied by cyanosis and lethargy, especially in infants. Auscultation of the chest may reveal crackles and wheezing, but it is often difficult to localize the source of these adventitious sounds in very young children with hyperresonant chests. It is often not possible to distinguish viral pneumonia clinically from disease caused by *Mycoplasma* and other bacterial pathogens.

Bacterial pneumonia in adults and older children typically begins suddenly with high fever, cough, and chest pain. Other symptoms that may be seen include drowsiness with intermittent periods of restlessness; rapid respirations; anxiety; and, occasionally, delirium. In many children, splinting on the affected side to minimize pleuritic pain and improve ventilation is noted; such children may lie on one side with the knees drawn up to the chest.

Physical findings depend on the stage of pneumonia. Early in the course of illness, diminished breath sounds, scattered crackles, and rhonchi are commonly heard over the affected lung field. With the development of increasing consolidation or complications of pneumonia such as pleural effusion or empyema, dullness on percussion is noted and breath sounds may be diminished. A lag in respiratory excursion often occurs on the affected side. Abdominal distention may be prominent because of gastric dilation from swallowed air or ileus. *Abdominal pain is common in lower-lobe pneumonia.* The liver may seem enlarged because of downward displacement of the diaphragm secondary to hyperinflation of the lungs or superimposed congestive heart failure.

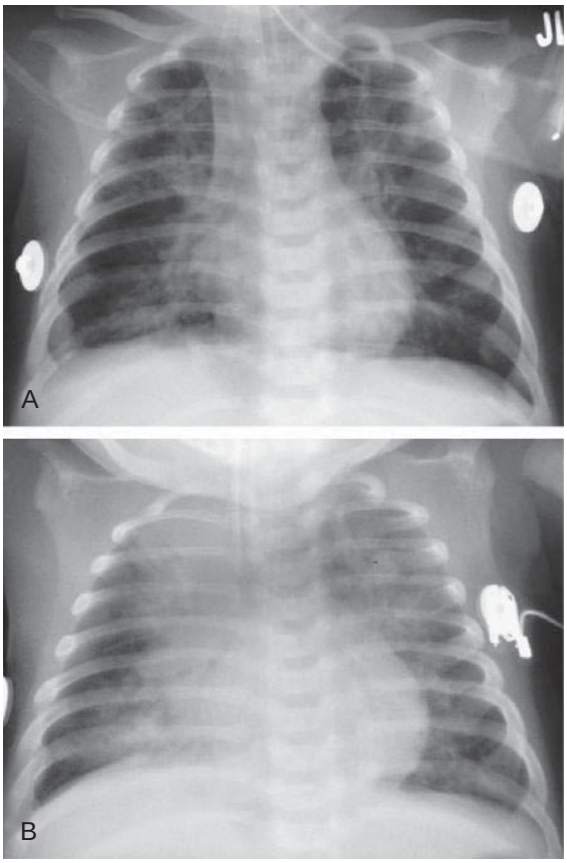

Figure 400-2 A, Radiographic findings characteristic of respiratory syncytial virus pneumonia in a 6 mo old infant with rapid respirations and fever. Anteroposterior radiograph of the chest shows hyperexpansion of the lungs with bilateral fine air space disease and streaks of density, indicating the 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.

Symptoms described in adults with pneumococcal pneumonia may be noted in older children but are rarely observed in infants and young children, in whom the clinical pattern is considerably more variable. In infants, there may be a prodrome of upper respiratory tract infection and diminished appetite, leading to the abrupt onset of fever, restlessness, apprehension, and respiratory distress. These infants appear ill, with respiratory distress manifested as grunting; nasal flaring; retractions of the supraclavicular, intercostal, and subcostal areas; tachypnea; tachycardia; air hunger; and often cyanosis. Results of physical examination may be misleading, particularly in young infants, with meager findings disproportionate to the degree of tachypnea. Some infants with bacterial pneumonia may have associated gastrointestinal disturbances characterized by vomiting, anorexia, diarrhea, and abdominal distention secondary to a paralytic ileus. Rapid progression of symptoms is characteristic in the most severe cases of bacterial pneumonia.

DIAGNOSIS

An infiltrate on chest radiograph (posteroanterior **and** lateral views) supports the diagnosis of pneumonia; the film may also indicate a complication such as a pleural effusion or empyema. Viral pneumonia is usually characterized by hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing (Fig. 400-2). Confluent lobar consolidation is typically seen with pneumococcal pneumonia (Fig. 400-3). The radiographic appearance alone is not diagnostic, and other clinical features must be considered. Repeat chest radiographs are not required for proof of cure for patients with uncomplicated pneumonia. Some

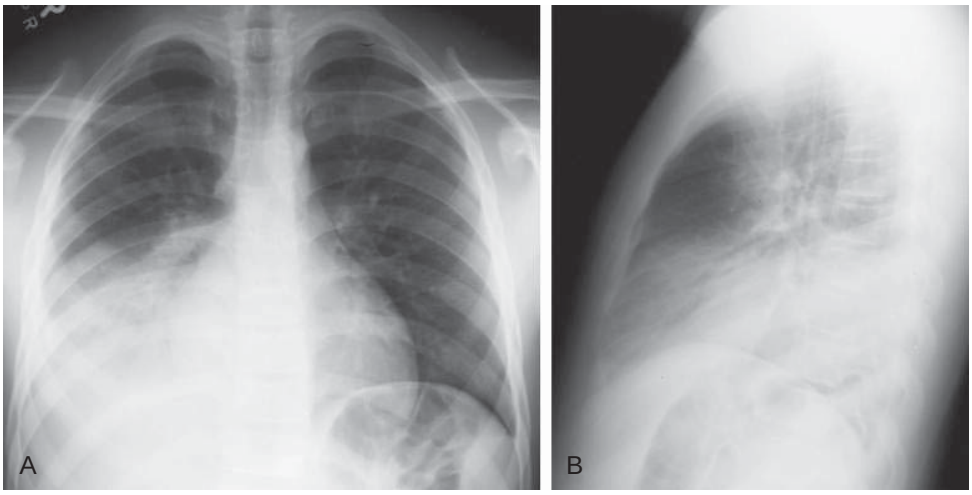

Figure 400-3 Radiographic findings characteristic of pneumococcal pneumonia in a 14 yr old boy with cough and fever. Posteroanterior **(A)** and lateral **(B)** chest radiographs reveal consolidation in the right lower lobe, strongly suggesting bacterial pneumonia.

experts suggest that a chest radiograph may not be necessary for older children with suspected pneumonia (cough, fever, localized crackles, or decreased breath sounds) who are well enough to be managed as outpatients.

Point-of-care use of portable or handheld ultrasonography is highly sensitive and specific in diagnosing pneumonia in children by determining lung consolidations and air bronchograms or effusions.

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/mm^3, with a lymphocyte predominance. Bacterial pneumonia is often associated with an elevated WBC count, in the range of 15,000-40,000/mm^3, and a predominance of granulocytes. A large pleural effusion, lobar consolidation, and a high fever at the onset of the illness are also suggestive of a bacterial etiology. **Atypical pneumonia** caused by *C. pneumoniae* or *M. pneumoniae* is difficult to distinguish from pneumococcal pneumonia on the basis of radiographic and laboratory findings, and although pneumococcal pneumonia is associated with a higher WBC count, erythrocyte sedimentation rate, procalcitonin, and C-reactive protein level, there is considerable overlap, particularly with adenoviruses and enteroviruses.

The definitive diagnosis of a viral infection rests on the isolation of a virus or detection of the viral genome or antigen in respiratory tract secretions. Reliable DNA or RNA tests for the rapid detection of many respiratory pathogens, such as mycoplasma, pertussis, and viruses, including RSV, parainfluenza, influenza, and adenoviruses, are available and accurate. Serologic techniques can also be used to diagnose a recent respiratory viral infection but generally require testing of acute and convalescent serum samples for a rise in antibodies to a specific viral agent. This diagnostic technique is laborious, slow, and not generally clinically useful because the infection usually resolves by the time it is confirmed serologically. Serologic testing may be valuable as an epidemiologic tool to define the incidence and prevalence of the various respiratory viral pathogens. Patient peripheral cell gene expression patterns determined by microarray reverse transcription polymerase chain reaction is an emerging technology that may help differentiate viral from bacterial causes of pneumonia.

The definitive diagnosis of a bacterial infection requires isolation of an organism from the blood, pleural fluid, or lung. Culture of sputum is of little value in the diagnosis of pneumonia in young children, while percutaneous lung aspiration is invasive and not routinely performed. Blood culture results are positive in only 10% of children with pneumococcal pneumonia and are not recommended for nontoxic appearing children treated as an outpatient. Blood cultures are recommended for those who fail to improve or have clinical deterioration, in those with complicated pneumonia (Table 400-5) and those requiring hospitalization. Cold agglutinins at titers >1:64 are found in the blood in ≈50% of patients with *M. pneumoniae* infections. Cold agglutinin findings are nonspecific because other pathogens such as influenza viruses may also cause increases. Acute infection caused by *M. pneumoniae* can be diagnosed on the basis of a positive polymerase chain reaction test result or seroconversion in an IgG assay. Serologic evidence, such as the antistreptolysin O titer, may be useful in the diagnosis of group A streptococcal pneumonia.

Table 400-5 Factors Suggesting Need for Hospitalization of Children with Pneumonia

Age <6 mo
Sickle cell anemia with acute chest syndrome
Multiple lobe involvement
Immunocompromised state
Toxic appearance
Moderate to severe respiratory distress
Requirement for supplemental oxygen
Complicated pneumonia*
Dehydration
Vomiting or inability to tolerate oral fluids or medications
No response to appropriate oral antibiotic therapy
Social factors (e.g., inability of caregivers to administer medications at home or follow-up appropriately)

*Pleural effusion, empyema, abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory distress syndrome, extrapulmonary infection (meningitis, arthritis, pericarditis, osteomyelitis, endocarditis), hemolytic uremic syndrome, sepsis.

Adapted from Baltimore RS: Pneumonia. In Jenson HB, Baltimore RS, editors: Pediatric infectious diseases: principles and practice, Philadelphia, 2002, WB Saunders, p. 801.

TREATMENT

Treatment of suspected bacterial pneumonia is based on the presumptive cause and the age and clinical appearance of the child. For mildly ill children who do not require hospitalization, amoxicillin is recommended. With the emergence of penicillin-resistant pneumococci, high doses of amoxicillin (80-90 mg/kg/24 hr) should be prescribed unless local data indicate a low prevalence of resistance. Therapeutic alternatives include cefuroxime axetil and amoxicillin/clavulanate. For school-age children and in children in whom infection with *M. pneumoniae* or *C. pneumoniae* is suggested, a macrolide antibiotic such as

azithromycin is an appropriate choice. In adolescents, a respiratory fluoroquinolone (levofloxacin, moxifloxacin) may be considered as an alternative. Despite substantial gains over the past decade, in developing countries only ≈60% of children with symptoms of pneumonia (≈50% in sub-Saharan Africa) are taken to an appropriate caregiver, and less than one-third receive antibiotics. The World Health Organization and other international groups have developed systems to train mothers and local healthcare providers in the recognition and treatment of pneumonia.

The empiric treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on the clinical manifestations at the time of presentation. In areas without substantial high-level penicillin resistance among *S. pneumoniae*, children who are fully immunized against *H. influenzae* type b and *S. pneumoniae* and are not severely ill should receive ampicillin or penicillin G. For children who do not meet these criteria, ceftriaxone or cefotaxime should be used. If clinical features suggest staphylococcal pneumonia (pneumatoceles, empyema), initial antimicrobial therapy should also include vancomycin or clindamycin.

If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for those patients who are mildly ill, have clinical evidence suggesting viral infection, and are in no respiratory distress. However, up to 30% of patients with known viral infection, particularly influenza viruses, may have coexisting bacterial pathogens. Therefore, if the decision is made to withhold antibiotic therapy on the basis of presumptive diagnosis of a viral infection, deterioration in clinical status should signal the possibility of superimposed bacterial infection, and antibiotic therapy should be initiated.

Table 400-5 notes the indications for admission to a hospital. The optimal duration of antibiotic treatment for pneumonia has not been well-established in controlled studies. However, antibiotics should generally be continued until the patient has been afebrile for 72 hr, and the total duration should not be less than 10 days (or 5 days if azithromycin is used). Shorter courses (5-7 days) may also be effective, particularly for children managed on an outpatient basis, but further study is needed. Available data do not support prolonged courses of treatment for uncomplicated pneumonia. In developing countries, oral zinc (10 mg/day for <12 mo, 20 mg/day for ≥12 mo) reduces mortality among children with clinically defined severe pneumonia.

PROGNOSIS

Typically, patients with uncomplicated community-acquired bacterial pneumonia show response to therapy, with improvement in clinical symptoms (fever, cough, tachypnea, chest pain), within 48-96 hr of initiation of antibiotics. Radiographic evidence of improvement lags substantially behind clinical improvement. A number of possibilities must be considered when a patient does not improve with appropriate antibiotic therapy: (1) complications, such as empyema (see Table 400-5); (2) bacterial resistance; (3) nonbacterial etiologies such as viruses or fungi and aspiration of foreign bodies or food; (4) bronchial obstruction from endobronchial lesions, foreign body, or mucous plugs; (5) preexisting diseases such as immunodeficiencies, ciliary dyskinesia, cystic fibrosis, pulmonary sequestration, or congenital pulmonary airway malformation, formerly called cystic adenomatoid malformation; and (6) other noninfectious causes (including bronchiolitis obliterans, hypersensitivity pneumonitis, eosinophilic pneumonia, aspiration, and granulomatosis with polyangiitis, formerly called Wegener granulomatosis). A repeat chest radiograph is the first step in determining the reason for delay in response to treatment. Bronchoalveolar lavage may be indicated in children with respiratory failure; high-resolution CT scans may better identify complications or an anatomic reason for a poor response to therapy.

Mortality from community-acquired pneumonia in developed nations is rare, and most children with pneumonia do not experience long-term pulmonary sequelae. Some data suggest that up to 45% of children have symptoms of asthma 5 yr after hospitalization for pneumonia; this finding may reflect either undiagnosed asthma at the time of presentation or a propensity for development of asthma after pneumonia.

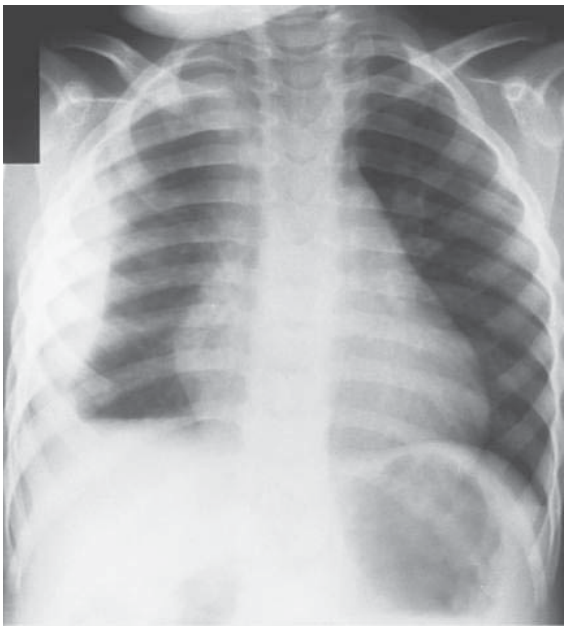

Figure 400-4 Pneumococcal empyema on the chest radiography of a 3 yr old child who has had upper respiratory symptoms and fever for 3 days. A pleural fluid collection can be seen on the right side. The patient had a positive pleural tap and blood culture result for pneumococci. The child recovered completely within 3 wk. *(From Kuhn JP, Slovis TL, Haller JO (eds):* Caffrey's pediatric diagnostic imaging, *ed 10, Philadelphia, 2004, Mosby, p. 1002.)*

COMPLICATIONS

Complications of pneumonia (see Table 400-5) are usually the result of direct spread of bacterial infection within the thoracic cavity (pleural effusion, empyema, and pericarditis) or bacteremia and hematologic spread (Fig. 400-4). Meningitis, 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* are the most common causes of parapneumonic effusions and empyema (Table 400-6). Nonetheless many effusions that complicate bacterial pneumonia are sterile. Universal 16S ribosomal RNA gene polymerase chain reaction identifies the bacterial genome and can determine the bacterial etiology of the effusion if the culture is negative. The treatment of empyema is based on the stage (exudative, fibrinopurulent, organizing). Imaging studies including ultrasonography and CT are helpful in determining the stage of empyema. The mainstays of therapy include antibiotic therapy and drainage with tube thoracostomy. Additional effective approaches include the use of intrapleural fibrinolytic therapy (urokinase, streptokinase, tissue plasminogen activator) and selected video-assisted thoracoscopy to debride or lyse adhesions and drain loculated areas of pus. Early diagnosis and intervention, particularly with fibrinolysis or less often video-assisted thoracoscopy, may obviate the need for thoracotomy and open debridement. Fibrinolysis is more cost-effective than video-assisted thoracoscopy.

PREVENTION

Some evidence exists to suggest that vaccination has reduced the incidence of pneumonia hospitalizations. The annual rate of all-cause pneumonia hospitalization among children younger than 2 yr of age in the United States during the period 1997-1999 was 12.5 per 1,000 children. In February 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was licensed and recommended. In 2006, the pneumonia hospitalization rate in this age group was 8.1 per 1,000 children, a 35% decrease from the prevaccine rate. Although these data do not establish that PCV7 directly reduced pneumonia hospitalization rates,

Table 400-6 Differentiation of Pleural Fluid

	TRANSUDATE	EMPYEMA
Appearance	Clear	Cloudy or purulent
Cell count (per mm^3)	<1,000	Often >50,000 (cell count has limited predictive value)
Cell type	Lymphocytes, monocytes	Polymorphonuclear leukocytes (neutrophils)
Lactate dehydrogenase	<200 U/L	More than two-thirds upper limit of normal for serum lactate dehydrogenase (LDH)
Pleural fluid:serum LDH ratio	<0.6	>0.6
Protein >3 g	Unusual	Common
Pleural fluid:serum protein ratio	<0.5	>0.5
Glucose*	Normal	Low (<40 mg/dL)
pH*	Normal (7.40-7.60)	<7.10
Gram stain	Negative	Occasionally positive (less than one-third of cases)
Cholesterol		>55 mg/dL
Pleural cholesterol:serum cholesterol ratio	<0.3	>0.3

*Low glucose or pH may be seen in malignant effusion, tuberculosis, esophageal rupture, pancreatitis (positive pleural amylase), and rheumatologic diseases (e.g., systemic lupus erythematosus).

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis & therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 30.*

they do suggest that vaccination has resulted in a sustained benefit in preventing hospitalization for young children with pneumonia.

In 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States; it may prevent even more cases of pneumococcal disease not covered by the PCV7 vaccine.

The expansion of influenza vaccine recommendations to include all children >6 mo of age in 2010 might be expected to affect pneumonia hospitalization rates in a similar fashion, and ongoing surveillance is warranted.

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