# Acute Pulmonary Infections

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## Contents




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**Learning Objectives**

- Describe the epidemiology of acute pulmonary infections that require pediatric intensive care.
- Describe the signs and symptoms of bronchiolitis and pneumonia.
- Explain host defense mechanisms during acute pulmonary infections.
- State the common etiologies of bronchiolitis.
- State the common etiologies of pneumonia.
- Describe the pathophysiology of bronchiolitis and pneumonia in children.
- Describe the treatment options, including modes of ventilation, for bronchiolitis and pneumonia.
- Summarize an effective management strategy for parapneumonic effusions and empyemas.

## 33.1 Introduction

Acute lower respiratory infection is a common cause of morbidity in infants and children and, at times, requires intensive care and mechanical ventilation. Viral bronchiolitis and bacterial pneumonia account for the majority of lower respiratory tract infections that lead to respiratory insufficiency and pediatric intensive care unit admission. Twenty-seven percent of children who require mechanical ventilation for at least 24 h in pediatric intensive care units are diagnosed with bronchiolitis, and 16% have the diagnosis of pneumonia. The median length of time intubated for an acute pulmonary infection leading to respiratory failure is approximately 7 days.



Viral bronchiolitis remains the leading cause for hospital admission in infancy; peak incidence is between 3 months and 6 months of age, and it is the most frequent cause of acute respiratory failure in children admitted to pediatric intensive care units in North America. Pneumonia in children younger than 5 years of age has an annual incidence of 34–40 cases per 1000 population at risk. Community-acquired pneumonia can also lead to severe respiratory compromise especially in children with preexisting disease. A detailed understanding of the diverse etiologies and distinct clinical courses of acute pulmonary infections is essential for the pediatric critical care practitioner. This chapter will focus on bronchiolitis and pneumonia as the two leading causes of pulmonary infections leading to PICU admission.

## 33.2 Bronchiolitis

### 33.2.1 Epidemiology

Mortality from RSV bronchiolitis continues to decline with better intensive care and the use of preventive therapies.

Approximately one-third of children develop bronchiolitis during the first 2 years of life, with peak incidence between 3 and 6 months of age. Of these, 2–3% require hospitalization, accounting for 16% to 18% of yearly hospitalizations. Overall mortality rate for all children remains low at 1–2% but as high as 5% in high-risk infants. Most deaths occur in infants younger than 6 months of age with comorbidities such as prematurity, congenital heart disease, congenital or acquired lung disease, or immunodeficiency.

### 33.2.2 Etiology of Viral Bronchiolitis

Bronchiolitis was originally described by Wilhelm Lange in 1901. Respiratory syncytial virus (RSV) was first isolated in 1957 and still represents the major cause of bronchiolitis. Other causative viruses include enterovirus/rhinovirus, influenza, human metapneumovirus, parainfluenza, adenovirus, coronavirus, and human bocavirus. In the northern hemisphere, RSV outbreaks occur from October to April and account for 40–80% of cases. Human rhinovirus/enterovirus is isolated from 15% to up to 39% of cases. Rhinovirus has a bimodal peak; the first is between April and May and then again between September and October. Human metapneumovirus (hMPV) was discovered in 2001 and is linked to approximately 7% of bronchiolitis infections. Parainfluenza infections peak at 10 months of age, representing approximately 3% of cases of bronchiolitis. Parainfluenza 3 (PIV-3) is endemic throughout the year but especially common in the late spring. Human bocavirus (HBoV) was identified in 2005 as a cause of upper respiratory infections. It is rarely isolated as a sole pathogen and instead is identified as a coinfection in bronchiolitis 80% of the time. While adenovirus has been associated with bronchiolitis, it is more likely to cause a necrotizing pneumonia. Up to 30% of children are found to have coinfections with two viruses, most commonly RSV and rhinovirus.

Males are 1.5–2 times more likely to require hospitalization for bronchiolitis and are likely to have more severe disease. An X-linked genetic trait that results in a reduced tolerance to hypoxia has been postulated and would be consistent with the observation of increased mortality in newborn males with infant respiratory distress syndrome. Virtually all children by the age of 2 will have been infected with RSV, all children by the age of 5 will have been infected with hMPV, and all children by the age of 9 will have been infected with HBoV.

Male infants are more likely to require hospitalization and usually manifest more severe disease.

### 33.2.3 General Presentation and Pathophysiology

The classic presentation begins with nasal discharge progressing to lower respiratory tract symptoms of persistent cough, tachypnea, and increased work of breathing. The timing of symptoms is variable. Young infants may present with apnea prior to other respiratory symptoms. Auscultatory findings include inspiratory crackles and expiratory wheezing with the hallmark feature of minute-to-minute variability. Bronchiolitis is characterized by extensive inflammation and edema of the airways with increased mucus production and necrosis of airway epithelial cells. This cellular debris and mucus can plug the bronchiole lumen leading to obstruction and air trapping. About one-third of infants will have fever that is usually less than 39 °C. Although the majority of infants will have normal radiographs, infants with more severe disease will have peribronchial thickening, hyperinflation, and atelectasis, especially of the right upper lobe. The median duration of symptoms is 2 weeks. Risk factors for severe disease include chronic lung disease of prematurity, hemodynamically significant heart disease, immunodeficiency, neuromuscular disorders, and young infants with history of prematurity, especially <32 weeks gestation.

The remainder of the discussion on bronchiolitis is divided into RSV and non-RSV bronchiolitis. Although etiologic agents may differ, clinical courses are often similar.

### 33.2.4 Respiratory Syncytial Virus (RSV)

About one-half of all infants will be infected with RSV bronchiolitis in their first year of life; 3% will be hospitalized and 10% of hospitalized infants will require mechanical ventilation.

Respiratory syncytial virus (RSV) accounts for 50–80% of bronchiolitis, infecting one-half of all infants within the first year of life and hospitalizing approximately 120,000 infants yearly (about 3% of affected infants). Approximately 10% of these infants require mechanical ventilation with more than 200 deaths annually. Coinfection with either hMPV or rhinovirus occurs in 10–30% of young children.

Two types of RSV exist – types A and B. Type A is more common and is believed to cause more severe disease, although data is not conclusive. Both types may exist simultaneously in the community. Infants less than 1 year will typically shed the virus for about 9 days. Children with immunodeficiencies may shed the virus for months. The immune response varies with age and contributes to both termination of the disease and its pathologic features.

The virus is transmitted by respiratory droplets following close contact with infected persons or by contact with contaminated objects or surfaces. The mean incubation period is 4–6 days. There is a 45% RSV transmission rate within families and about one-half of hospital workers will acquire RSV. Therefore, hand washing and the wearing of gowns and gloves is of primary importance to attenuate transmission.

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### 33.2.5 Pathophysiology

#### 33.2.5.1 Antibody-Mediated Immunity

RSV introduced onto the nasal or conjunctival mucosal surface causes profuse rhinorrhea within a few days. During the first 2 months of life, passively acquired maternal antibodies are protective. However, as maternal antibody titers gradually decrease, infants become susceptible to severe disease. Cell-bound IgA may develop to help clear the virus. Circulating IgG directed against the glycoprotein (G) and fusion (F) proteins (operative in syncytia formation) on the viral surface will develop several days later. Infants less than 3 months of age appear to induce a weaker antibody response likely due to the presence of maternal antibodies. Virus-specific IgE in the respiratory tract is associated with disease severity. Often, complete and effective immune responses are not induced; thus reinfections are possible even during the same season.

#### 33.2.5.2 Cell-Mediated Immunity

Upregulation of the inflammatory cascade with release of chemokines and cytokines is contributory to the airway inflammation and hyperreactivity.

Epithelial cells and alveolar macrophages are key activators of cellular immunity. Although these cells enhance viral clearing, they also contribute to airway inflammation through the release of cytokines and chemokines. These include interleukin (IL)-1, tumor necrosis factor-alpha, IL-6, IL-8, macrophage-inflammatory protein (MIP)-1-alpha, and RANTES (regulated upon activation, normal T cell expressed and secreted). Release of these cytokines and chemokines is believed to be partially responsible for airway inflammation and hyperreactivity. The effects of these mediators persist beyond the acute infection and contribute to prolonged pulmonary dysfunction.

Children who require mechanical ventilation have lower peripheral T cell counts compared to hospitalized infants not requiring mechanical ventilation. Mechanically ventilated infants demonstrate low T cell proliferative responses and interferon (IFN-γ) production. IL-12 is required for the initiation of cellular immunity. The duration of mechanical ventilation was found to be inversely related to IL-12 production. The role of Th1-/Th2-like cytokine profiles, expressed as IFN-γ/IL-4 ratios, is controversial. In some studies, these

ratios decreased after polyclonal stimulation in hospitalized infants with RSV. However, more recent studies have shown normal ratios following polyclonal stimulation.

Neutrophils are the predominant cell found in the airways of infants with RSV bronchiolitis. IL-8 is found in high concentrations in the nasal secretions of infected children and acts as a neutrophil chemoattractant. Further evidence of cellular induced injury is seen in postmortem examination where peribronchial lymphocyte infiltration with bronchial epithelial necrosis is typically present.

### 33.2.6 Clinical Presentation and Course

Infants typically present with tachypnea, rhinorrhea, cough, low-grade fever, irritability, poor feeding, and vomiting. Respiratory rates greater than 60 breaths per minute are often associated with room air oxygen saturations of less than 96%. Infants may also have tachycardia, mild conjunctivitis, otitis media, or pharyngitis. Low-grade fever usually persists for 1–3 days. In addition, infants may develop a metabolic acidosis from poor caloric and fluid intake.

Apnea often is the first presenting symptom of RSV bronchiolitis in small infants. The etiology of apnea remains unknown; however, it is likely related to the immaturity of the respiratory control center in the brainstem. The incidence of apnea in infants with bronchiolitis is approximately 16–20%.

The heterogeneous nature of RSV-induced lung disease can cause atelectasis in some areas and overdistension in others. Chest roentgenograms often show hyperinflation with flattening of the diaphragms and patchy or peribronchial infiltrates. Atelectasis, especially of the right upper lobe, is often seen. Infants may have high lung volumes with the functional residual capacity often being twice normal. The decrease in dynamic compliance and increase in airway resistance leads to marked increase in work of breathing, often worse during expiration due to lower airway obstruction. Alterations in gas exchange and hypoxemia are secondary to a ventilation-perfusion mismatch.

The anatomical differences between young infants and older children contribute to the severity of the disease in the young. Due to the highly compliant cartilaginous chest wall and underdeveloped thoracic musculature, the infant's chest wall has difficulty countering the lung's inherent tendency toward collapse. Infants' smaller airways are more easily obstructed by secretions. These characteristics lead to a greater propensity toward atelectasis. The absence of effective collateral ventilation in infants also contributes to the development of atelectasis and impaired gas exchange. Cellular debris in small airways and peribronchial edema increase airway resistance leading to wheezing as the predominant symptom in some infants.

Despite the potential for severe impairment in lung function, most hospitalized infants improve within 3–5 days. Typically, by 2 weeks, they have normal respiratory rates, oxygenation, and ventilation. Chest radiographs usually normalize by day 9. However, about 20% of infants will have a protracted course, with some mild respiratory symptoms persisting for months.

Viral respiratory infections have been linked to the development of asthma later in childhood. The Tucson Children's Respiratory Study group prospectively followed for 13 years 880 infants who had bronchiolitis and found an increased risk for subsequent wheezing episodes. Additional studies including the Danish Copenhagen Prospective Study of Asthma in Childhood and COAST study support the hypothesis that early viral infections are a marker of

atopic predisposition. Both hypotheses may be correct with two different mechanisms at play. Seasonal RSV infections can produce a cytopathic effect in the airways, and rhinovirus outbreaks throughout the year often are associated with a family history of asthma or atopy.

### 33.2.7 High-Risk Populations

Some infants are at an increased risk for severe RSV disease such as those with chronic lung disease due to prematurity (bronchopulmonary dysplasia), cystic fibrosis, congenital heart disease, and immunodeficiencies. In children with cystic fibrosis, RSV accounted for 18% of symptomatic infections, 33% of hospitalizations for infants less than 1 year, and 43% of infants requiring mechanical ventilation. In a study of hospitalized infants with congenital heart disease (primarily cyanotic lesions or pulmonary hypertension) infected with RSV, 33% required intensive care, 19% received mechanical ventilation, and 3.4% died. Children having undergone hematopoietic stem cell transplants who develop RSV infections have an extremely high mortality of 60–80% despite mechanical ventilation and antiviral therapy. Environmental factors such as crowding, passive exposure to tobacco smoke, and lack of breast-feeding are associated with the development of severe disease. Compared to national averages, Native American and Alaskan children younger than 1 year of age have higher rates of infections.



### 33.2.8 Non-RSV Bronchiolitis

#### 33.2.8.1 Rhinovirus/Enterovirus

Rhinovirus (RV) and enterovirus (EV) are leading causes of upper respiratory tract infections worldwide. After RSV, they are the most common viruses detected in hospitalized children. There are three distinct RV – A, B, and C – and four EV: A, B, C, and D. In 2014, EV-D68 was isolated as the cause for a large nationwide (49 states and the District of Columbia) outbreak in the US pediatric population. The RV and EV are closely related genetically and hence are not differentiated by nucleic acid amplification by PCR due to cross-reactivity of the assay. Children are the major reservoir and experience up to 8–12 infections per year. Infections occur all year but have two peaks: the first in April to May and the second from September to October. RV-C may peak more in the winter months and may contribute to more severe lower respiratory tract infections in children. RVs enter via the upper respiratory tract and bind to respiratory epithelial cells via several receptors, depending on the species. This attachment elicits an innate immune response leading to airway inflammation and remodeling. Until recently, RVs were thought to only infect the upper respiratory tract, but studies have demonstrated susceptibility of bronchial epithelial cells. Preexisting epithelial injury enhances RV replication, which may explain more severe disease in children with asthma or preexisting lung disease. RV tends to affect older children and has a milder and shorter clinical course in previously healthy children. However, as RV/EV often affects children with underlying cardiorespiratory or immunocompromised conditions, their clinical course may be more severe.

#### 33.2.8.2 Parainfluenza

There are three subtypes of human parainfluenza viruses. PIV-3 (occurs late spring to early summer each year) is most frequently isolated from children with bronchiolitis, while PIV-1 (occurring in the fall of odd years) and PIV-2 (occurs in fall each year) most commonly cause croup. About 25% of children with PIV bronchiolitis admitted to the hospital require oxygen therapy, and 3% were admitted to the intensive care unit. Similar to RSV, both cell-mediated hyper-responsiveness to viral antigen and virus-specific IgE responses are observed in children with parainfluenza bronchiolitis. Upper airway edema with concomitant obstructive symptoms may be present.

#### 33.2.8.3 Metapneumoviruses

The human metapneumoviruses (hMPV) are a group of RNA viruses of the *Paramyxoviridae* family identified in humans in 2001. There are two major genetic lineages, A and B. Although both genotypes can co-circulate, the dominant lineage may vary year to year. Group A is associated with more severe clinical symptoms. Infection has a seasonal distribution similar to RSV and influenza. The majority of children are born with maternal hMPV-specific IgG which wanes to around 25% by 6–12 months of age. By age 5, essentially 100% of children have been exposed to hMPV and will have neutralizing antibody to hMPV. Clinical presentation of children with this virus is similar to RSV. The pulmonary inflammation generally peaks on day 5 which includes interstitial edema and inflammatory cell infiltrates of the bronchioles and alveoli. These inflammatory changes can persist for up to 21 days. About half of infected children are 0–12 months of age. Immunity is incomplete and reinfections occur throughout adult life.

#### 33.2.8.4 Human Bocavirus

Human bocavirus (HBoV) was discovered in 2003. With amino acid sequencing, this new member of the *Parvoviridae* family was found to be closely related to the bovine parvovirus and the canine minute virus, hence the name bocavirus (BO for bovine and CA for canine). The seasonality is unclear but appears to involve primarily the colder months. It remains undetermined if HBoV is a primary pathogen or acts to exacerbate other viral illnesses. Studies have reported HBoV in approximately 3% of children with respiratory tract infections. In a cohort of pediatric patients in Quebec, HBoV was detected in 14% of symptomatic children and 43% of asymptomatic children. A coinfection was detected in 71% of patients, consistent with other studies reporting 35–90% coinfection rates. Where earlier studies detected very low (1%) detection of HBoV DNA in asymptomatic patients, these tests were performed on nasal swabs. The Quebec cohort analyzed nasopharyngeal aspirates or bronchoalveolar lavage samples, supporting an increased incidence in the lower respiratory tract. In their population, none of the children with isolated HBoV infection required admission to the intensive care unit. Other studies have identified only HBoV as the causative agent in bronchiolitis and support that these patients generally have milder clinical symptoms. The pathogenesis of HBoV has not been well described, but with the high occurrence of wheezing and lower respiratory tract symptoms in children infected with the virus, it is speculated that this virus may be a significant contributor to asthma exacerbations. The majority of infected children have rhinorrhea, cough, and wheezing; however, diarrhea has been reported in up to 25% of these children. In children with high viral loads, HBoV has been detected in the serum suggesting the potential for disease beyond the respiratory tract.

#### 33.2.8.5 Coronavirus

Human coronaviruses (CoV) were first described in the 1960s in patients with the common cold. In humans, CoV infections primarily involve the upper respiratory tract and the gastrointestinal tract with varying disease severity ranging from the common cold to bronchiolitis and pneumonia. In general, CoV infections occur in the winter season in temperate climates. The typical clinical course lasts several days and is indistinguishable from other viral respiratory pathogens. More recently, two strains of CoV were discovered that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which are discussed in the viral pneumonia section.

#### 33.2.8.6 Influenza A and B

Both influenza A, including novel influenza strains such as H1N1, and influenza B can cause a clinical picture consistent with bronchiolitis in the small infant. These viruses may cause severe multisystem disease and are discussed in greater detail in the viral pneumonia section.

#### 33.2.8.7 Diagnosis

Molecular assays are the recommended test for respiratory virus detection. The published sensitivities and specificities approach 100% when compared to tissue culture or antigen assay. These assays generally use nucleic acid amplification by polymerase chain reaction. The assay results are available in 30–60 min. The most important cause of false-negative test results remains poor specimen handling or inadequate sample collection. Other than aiding with cohorting of hospitalized patients, detection and identification of respiratory viruses is rarely clinically useful.



#### 33.2.8.8 Treatment

Regardless of the viral etiology of bronchiolitis, supportive care remains the mainstay of treatment (◘ Table 33.1). Supplemental humidified oxygen is frequently needed. Titrating oxygen to maintain oxygen saturations at 90% is shown to be safe and provide adequate tissue oxygenation. It is common for infants and children to have intermittent, brief episodes of hypoxemia that, if left untreated, does not cause impairment in intellect or behavior. As many infants are obligate nasal breathers, nasal suctioning may be beneficial to maintain an unobstructed upper airway. A retrospective study reported that deep suctioning was associated with longer lengths of stay; thus, routine deep suctioning may not be beneficial. A Cochrane review found no benefit in chest physiotherapy by vibration, percussion, or passive expiratory techniques.

The affected infant or child is often unable to take adequate fluids complicated by increased insensible losses from the respiratory tract. About one-third of infants hospitalized with bronchiolitis require intravenous fluids. Stable infants, especially those with respiratory rates exceeding 60–70 breaths per minute, are often not able to take adequate feeds, but generally tolerate nasogastric feeds. Infants and children with severe respiratory distress should be kept NPO in the event respiratory failure ensues and endotracheal intubation is required. Some infants and children may develop fluid retention secondary to increased production of antidiuretic hormone.

Supportive therapy is the mainstay of treatment for bronchiolitis. Ribavirin, bronchodilators, and corticosteroids have not shown benefit.

Antibiotics are not routinely indicated in previously healthy children. In a 9-year prospective study of 565 children with RSV by Dr. Hall, a concurrent bacterial infection was found in only 1.2%. However, the incidence of bacterial coinfection may be increased in infants and children who develop respiratory failure requiring mechanical ventilation. The Royal Liverpool Children's Hospital group collected lower airway secretions by bronchoalveolar lavage

**Table 33.1** 2014 AAP clinical practice guidelines

| | |
|---|---|
| 1 | Clinicians should not administer albuterol to infants and children with bronchiolitis |
| 2 | Clinicians should not administer epinephrine to infants and children with bronchiolitis |
| 3a | Nebulized hypertonic saline should not be administered to infants with bronchiolitis in the ED |
| 3b | Clinicians may administer nebulized hypertonic saline to hospitalized infants and children with bronchiolitis |
| 4 | Clinicians should not administer systemic corticosteroids to infants and children with bronchiolitis |
| 5a | Clinicians may choose to not administer supplemental oxygen if oxyhemoglobin saturations exceed 90% in infants and children with bronchiolitis |
| 5b | Clinicians may choose not to use continuous pulse oximetry for infants and children with bronchiolitis |
| 6 | Clinicians should not use chest physiotherapy for infants and children with bronchiolitis |
| 7 | Clinicians should not administer antibacterial medications to infants and children with bronchiolitis unless there is a concomitant bacterial infection or strong suspicion of one |
| 8 | Clinicians should administer nasogastric or intravenous fluids for infants and children with bronchiolitis who cannot maintain hydration orally |

(BAL) within 3 h of endotracheal intubation in 165 infants and children with documented RSV infections. Twenty-one percent were found to have a coinfection with $>10^5$ cfu/mL bacteria. Of the 98 children in this study with any bacteria isolated by BAL, 23% had multiple organisms. Interestingly, 45% of these patients had received antibiotics prior to endotracheal intubation. Dr. Hall and colleagues also found a significantly greater proportion of bacterial infections occurring in children who had received parenteral antibiotics. An abnormal white blood cell count is not useful for predicting a concurrent bacterial infection. Approximately 25% of hospitalized infants with bronchiolitis will have radiologic evidence of atelectasis, making it difficult to distinguish a bacterial infiltrate or consolidation. Procalcitonin concentrations >1 ng/L have shown some promise in differentiating viral and bacterial pneumonia.

High-risk patients often require close monitoring and care in an intensive care unit. These include infants less than 6 weeks of age or infants with a history of prematurity, congenital heart disease, bronchopulmonary dysplasia, immunodeficiency, or neurologic disease. Infants with RSV bronchiolitis typically have a combination of hyperinflation, pulmonary infiltrates, and atelectasis. Therefore, no one mode of ventilation can be recommended for all infants. Humidified, heated high-flow nasal cannula (HFNC) to deliver air-oxygen mixtures can improve respiratory effort and generate positive airway pressure. Evidence suggests it reduces work of breathing and may decrease the need for intubation. Other noninvasive positive pressure (NIPP) modes (CPAP or BiPAP) may be attempted in infants and children where their primary respiratory embarrassment is secondary to atelectasis. However, this may not be suitable if the disease process appears severe or protracted as prolonged use of NIPP may make feeding difficult, cause breakdown of facial tissue, or be dif-

ficult to maintain without significant sedation that further compromises ventilation. If an infant requires endotracheal intubation, the mode of mechanical ventilation should be tailored to the predominant lung pathology present (i.e., atelectasis versus hyperinflation). Children with significant air trapping may need mechanical ventilation similar to a child with asthma, providing relatively low respiratory rates and longer inspiration and exhalation times. The more typical infant loses functional residual capacity (FRC) because of atelectasis and alveolar infiltrates. Therefore, despite having some air trapping, these infants often need PEEP adjusted to recruit alveoli and return FRC to normal. In the setting of elevated pulmonary vascular resistance (PVR) that may occur in infants with congenital heart disease or bronchopulmonary dysplasia, lowering PVR by traditional methods such as maintaining oxygenation, deep sedation, muscle relaxation, and even nitric oxide may be indicated.

Ribavirin is the only FDA-approved antiviral drug for RSV. Ribavirin inhibits viral replication and is active against RSV, influenza A and B, adenoviruses, and hepatitis viruses. For lower respiratory tract diseases, ribavirin is typically administered via aerosolization. In 1996, a meta-analysis of studies involving ribavirin was discouraging and was consistent with the common clinical experience that ribavirin did not improve clinical outcomes. Therapy targeted at attenuating the virus-induced inflammatory cascade has also been disappointing. Corticosteroid administration was not associated with reduction in clinical scores, the need for hospitalization, or the length of hospitalization. Routine use of any corticosteroid given via any route (intravenous, enteral, or aerosolized) is not indicated, except in patients with preexisting chronic lung disease.



Bronchodilators have not shown a clear benefit in patients with acute RSV bronchiolitis. In 12 randomized controlled trials involving 843 infants, evaluating the effect of salbutamol or albuterol on bronchiolitis, 9 (75%) showed no effect. The remaining three studies demonstrated only a small transient improvement in the acute clinical score. The original AAP clinical guidelines included a trial of β-adrenergic agonists as an option. However, given additional evidence demonstrating no benefit, this recommendation has been removed. It is recognized that a small subset of children may have reversible airway smooth muscle constriction responsive to β-adrenergic agonists. Also, children with severe disease or with respiratory failure were excluded from all these trials, so evidence cannot be generalized to this population.

A recent Cochrane meta-analysis found no evidence to support the use of nebulized epinephrine for inpatients. Two large multicenter randomized trials of nebulized epinephrine found no improvement in length of stay or outcomes when compared to placebo or albuterol. Evidence remains controversial regarding its use in the outpatient setting where a systematic review concluded that it might reduce hospitalizations.

Nebulized hypertonic saline increases mucociliary clearance in both normal and diseased lungs. With inflammation and mucus plugging prominent in bronchiolitis, hypertonic saline should be beneficial. Studies have shown it to be safe and effective in improving symptoms in mild-to-moderate bronchiolitis. However, a 2013 Cochrane review along with additional randomized controlled studies did not demonstrate a significant decrease in the length of hospitalization or in reducing hospital admissions. Like many other treatments, its use has not been studied in the intensive care setting.

Several studies evaluated the benefit of surfactant and nitric oxide for severe respiratory distress. There are a few preliminary studies that report inhaled nitric oxide to be safe and possibly decrease length of hospitalization. A Cochrane review of surfactant for the treatment of bronchiolitis also showed a

favorable effect on duration of mechanical ventilation, duration of ICU stay, as well as improved oxygenation and ventilation. However, the number of studies was small with only 79 subjects in total. Heliox, a mixture of oxygen (20–30%) and helium (70–80%) resulting in lower viscosity than air, has been used successfully in cases of airway obstruction, croup, airway surgery, and asthma to reduce respiratory effort during the period of airway compromise. A Cochrane review of 447 infants with viral bronchiolitis suggested a reduced clinical score for respiratory distress in the first hour after starting heliox treatment, but did not show a decrease in intubation rate or in the length of treatment.

### 33.2.8.9 Prevention

Palivizumab should be used as preventive therapy in infants with chronic lung disease and congenital heart disease. Cardiopulmonary bypass significantly lowers the serum level of palivizumab, so it should be redosed following surgery if continued protection is desired.

Palivizumab (Synagis™) is a neutralizing humanized mouse monoclonal antibody directed against the RSV-F glycoprotein. It was licensed by the Food and Drug Administration (FDA) in 1998 for premature infants and infants with bronchopulmonary dysplasia. The randomized, double-blind, placebo-controlled IMpact-RSV trial involving 1502 high-risk infants found a significant (55%) reduction in hospitalizations. With the exception of very rare anaphylaxis, no significant adverse effects have been observed. Palivizumab has been approved for use in infants with congenital heart disease. The cardiac Synagis study group included 1287 children with congenital heart disease in a randomized, double-blind, placebo-controlled trial; it found a 45% relative reduction in RSV-associated hospitalizations with no deaths attributable to the palivizumab. Since cardiopulmonary bypass can decrease serum drug concentrations by about 58%, it is recommended that an additional dose be given following cardiac surgery, if continued protection is desired.

In 2014, the American Academy of Pediatrics updated the guidelines for the administration of palivizumab (Table 33.2). It should be administered intramuscularly as 15 mg/kg every 30 days for a total of five doses during RSV season, which is generally from November through March, to high-risk infants. This includes preterm infants born before 29 weeks, infants with hemodynamically significant congenital heart disease, and infants with chronic lung disease

**Table 33.2** 2014 AAP clinical practice guidelines for prevention

| | |
|---|---|
| 1 | Clinicians should administer palivizumab during the first year of life to infants with gestational age <29 weeks, 0 days |
| 2 | Clinicians should administer palivizumab during the first year of life to infants with hemodynamically significant heart disease |
| 3 | Clinicians may administer palivizumab during the first year of life to infants with chronic lung disease of prematurity defined as preterm infants <32 weeks, 0 days gestation who require >21% oxygen for at least the first 28 days of life |
| 4 | Clinicians should administer a maximum of five monthly doses (15 mg/kg/dose) of palivizumab during the respiratory syncytial virus season |
| 5 | All people should disinfect hands before and after direct contact with patients, inanimate objects in the direct vicinity of the patient, and after removing gloves |
| 6 | All people should use alcohol-based rub for hand decontamination; if not available, wash with soap and water |
| 7 | Clinicians should counsel about the harm from exposing infants or children to cigarette smoke |
| 8 | Clinicians should encourage breast-feeding for at least 6 months to decrease morbidity of respiratory infections |

of prematurity that required oxygen for >28 days. These infants should also receive palivizumab in their second year of life if they continue to require oxygen, diuretics, or corticosteroids. Infants or children who develop an RSV infection should continue to receive prophylaxis following recovery because the naturally acquired antibodies are not fully protective.

## 33.3 Pneumonia

Pneumonia describes any inflammatory condition of the lung involving the alveoli. In response to inflammation, the alveoli become filled with inflammatory fluid, inflammatory cells, and cellular debris. Infection is the primary cause of parenchymal injury to the lung. Causative pathogens include viruses, bacteria, and fungi. Alveolar inflammation may also result from aspirated foreign matter.

### 33.3.1 Clinical Presentation



Signs and symptoms of pneumonia are nonspecific and may be occult in the young infant. Children often have fever, chills, headache, malaise, restlessness, and irritability. Gastrointestinal complaints such as abdominal pain, distention, or emesis may also be present in young children. The symptoms are often preceded by minor upper respiratory tract infections characterized by low-grade fever and rhinorrhea. With more significant involvement of the lower respiratory tract, tachypnea, dyspnea, cough, nasal flaring, grunting, or retractions may be seen. The older child may demonstrate productive sputum and complain of pleuritic chest pain. On auscultation of the chest, crackles and/or decreased breath sounds might be heard over areas of consolidation or pleural effusions. However, due to the short path for transmission of breath sounds and the small chest size in infants, breath sounds may not be decreased, even in the presence of effusions. Children with pleural irritation might prefer to lie on the affected side with legs flexed and may complain of radiating pain to the neck and shoulder or into the abdomen. A systematic review suggests that hypoxemia, altered mental status, age < 6 months, dyspnea, multilobar infiltrates, and moderate/large pleural effusions are the factors most predictive of pneumonia severity in children.

### 33.3.2 Epidemiology

Community-acquired pneumonia (CAP) is defined as an acute infection of the lung parenchyma that was acquired outside the hospital. It is a common, and at times, a serious infection in children. The incidence has decreased substantially in recent decades due to improved socioeconomic conditions, better access to care, implementation of effective management and preventive strategies, and development of vaccines. The Global Burden of Diseases study estimated that pneumonia accounted for almost 900,000 of the 6.3 million deaths in children in 2013. The incidence of pneumonia in children under 5 years of age in affluent countries is estimated at 0.015 episodes per child year compared to 0.22 episodes per child year in low- and middle-income countries. The exact prevalence of the etiologic agents causing pediatric pneumonia is difficult to ascertain. It is often difficult to differentiate viral from bacterial pneumonia

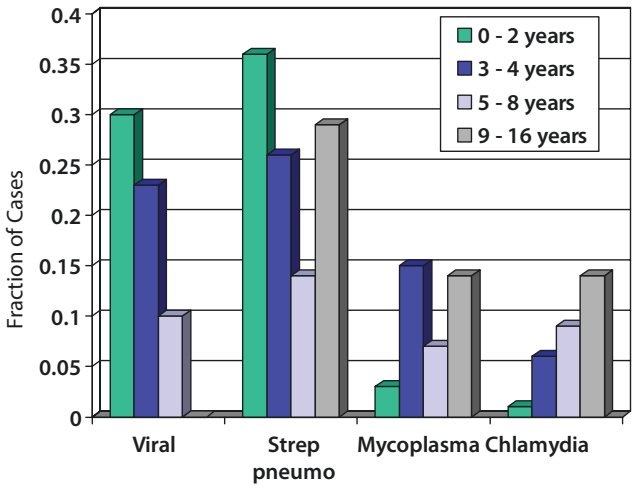


**Fig. 33.1** Etiology of community-acquired pneumonia based on age

based solely on clinical examination. Specific pathogens causing CAP can be determined in only approximately one-third of children using commonly available cultures, antigen detection, or serologic techniques. Blood cultures yield pathogens in only about 10% of infants and children with bacterial CAP. With these inherent limitations, it is generally thought that viruses account for approximately 80% of CAP in children under the age of 2 years and approximately 50% of CAP in preschool children ages 2–5 years. Viral causes decline in the school age and adolescent child, and bacterial causes such as *Streptococcus pneumoniae* and *Mycoplasma* become important pathogens (Fig. 33.1).

It is difficult to determine the etiologic agent causing pneumonia, but when microbial agents are identified, bacteria are isolated in 20–30%.

Overall, bacteria may account for 15–20% of community-acquired pneumonias; however, it is often not possible to distinguish colonization from pathogenic bacteria. More recent meta-analyses suggest that clinical pneumonia may be caused by sequential or concurrent organisms. Severe disease is often caused by multiple pathogens. The likelihood of infection with different bacteria varies by age. In the newborn period, organisms from the maternal genital tract are likely causes and include *Group B Streptococcus*, *Escherichia coli*, enteric Gram-negative bacilli, *Listeria*, and *Chlamydia*. In older infants, *Streptococcus pneumoniae* becomes a significant cause. *Group A Streptococcus* and *Staphylococcus aureus* are uncommon causes. *Moraxella catarrhalis* is a common cause of upper respiratory tract disease but rarely causes pneumonia. About 20% of infants with pertussis will have bacterial coinfection. In children older than 6 years of age, *Streptococcus pneumoniae* remains the most common cause. *Haemophilus influenzae type B* (HIB), and most recently *Streptococcus pneumoniae*, have decreased significantly as causes of CAP due to the widespread use of effective vaccines.

In the older child and young adolescent, the atypical pneumonias, *Mycoplasma* and *Chlamydia*, become more prevalent and viral causes less common. Rare bacterial pneumonias can occur with animal contact and include *Francisella tularensis* (rabbits), *Chlamydia psittaci* (parrots and birds), *Coxiella burnetii* (sheep), and *Salmonella choleraesuis* (pigs). Children with congenital anatomical defects, immunodeficiencies, neurologic disorders, and genetic disorders are at increased risk for bacterial, viral, and fungal pneumonia.

### 33.3.3 Normal Host Defense Mechanisms

The airways are normally sterile below the sublaryngeal area to the lung parenchyma. There are several protective mechanisms that include anatomic and mechanical factors, local immune defenses, and the systemic immune response. Microbes are filtered by nasal hairs or are expelled from the airways by the epiglottic reflex, cough reflex, and mucociliary apparatus. Immunoglobulin A (IgA) is the predominant immunoglobulin present in the upper respiratory tract. IgA is able to bind two antigens simultaneously, forming large antigen-antibody complexes. In this manner, the microbes are neutralized and removed by ciliary clearance, thus preventing microbial binding to the epithelium. In the lower tract, immunoglobulin G (IgG) provides humoral protection by opsonizing microbes for phagocytosis by neutrophils and macrophages, activating the complement cascade, and by neutralizing bacterial endotoxin. Activated alveolar macrophages and/or neutrophils produce superoxide anions, hydrogen peroxide, and hydroxyl radicals that serve an important role in the host defense; however, uncontrolled production can lead to lung injury. In addition to oxygen radicals, a number of cytokines are produced by the alveolar macrophages. These include IL-1, IL-6, IL-17, TNF, transforming growth factor-β (TGF-β), chemotactic factors, platelet-derived growth factor, and macrophage colony-stimulating factor (M-CSF). These cytokines play a central role in phagocytic recruitment and activation.

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Pneumonia occurs when one or more of the host defense mechanisms are altered. Viruses enhance the host susceptibility to bacterial pathogens by affecting clearing mechanisms and by weakening the host immune response.

Infection occurs when one or more of the defense mechanisms are impaired, invasion by a virulent organism, and/or if the infectious inoculum overwhelms the defense mechanisms. Pathogens typically gain entry through inhalation of aerosolized material or through aspiration of resistant organisms inhabiting the upper airways. Less frequently, pneumonia can occur via hematogenous spread.

In children with bacterial pneumonia, a significant portion will have a concurrent or preceding viral infection. Viral infection may predispose to bacterial superinfection by reducing clearance mechanisms, weakening the host immune response, and allowing direct access via necrosis of the bronchial epithelium.

### 33.3.4 Pathophysiology

Pathogens entering the lower airways evoke an exudative consolidation of pulmonary tissues. Initially, there is hyperemia of lung parenchyma due to vascular engorgement and capillary leak causing exudation and intra-alveolar fluid accumulation. Fibrin is then deposited and the airways are infiltrated with neutrophils. Consolidation decreases lung compliance, vital capacity, and the alveolar surface area available for gas exchange. A physiologic shunt (V/Q mismatch) occurs as there is increased blood flow through poorly ventilated segments of the lung, resulting in hypoxemia. Compensatory hypoxic vasoconstriction may occur in an attempt to reduce V/Q mismatch and hypoxemia, especially in localized areas of consolidation.

With treatment, resolution of consolidation occurs in 8–10 days. The exudate undergoes enzymatic digestion and is either reabsorbed or removed by coughing. If the bacterial infection extends into the pleural cavity, an empyema may result.

## 33.4 Specific Etiologies

### 33.4.1 Bacterial Pneumonia

#### 33.4.1.1 Streptococcus pneumoniae

*Streptococcus pneumoniae* is the most common bacterial cause for pneumonia.

*Streptococcus pneumoniae* is a Gram-positive diplococcus that is frequently found in the upper respiratory tract. There are over 80 capsular serotypes with 80% of infections caused by 14 serotypes. It is the most common bacterial cause for pneumonia occurring at a peak age of 13–18 months. Typically, it causes a lobar or segmental consolidation, but it may manifest as patchy infiltrates in infants. Pleural effusions occur in up to 20–60% of children who require hospitalization (◘ Fig. 33.2). Pneumatocele formation is rare. Hemolytic uremic syndrome is associated with neuraminidase-producing strains.

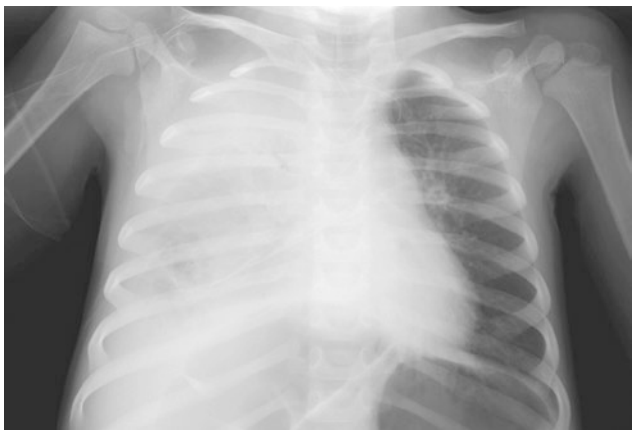
Treatment is typically with a penicillin or cephalosporin. Emerging antibiotic resistance may require initial therapy with vancomycin. In hospitalized patients, parenteral therapy is generally needed for 48–72 h after fever resolves, followed by completion of 7–10 days of enteral therapy.

Pneumococcal conjugate vaccines (PCVs) have been developed that confer immunity against 13 and 23 serotypes. The 13-valent PCV (Prevnar 13) was licensed for use in the United States in 2010. The PCVs have been highly effective at reducing hospitalizations for pneumococcal pneumonia.

PCV is now recommended universally for children younger than 24 months of age. The 23-valent PCV (Pneumovax) is available for high-risk children. This includes children with sickle cell disease and other types of functional asplenia, human immunodeficiency syndrome, and primary immunodeficiency, children receiving immunosuppressive therapy, and children with chronic pulmonary or cardiac disease. Children with sickle cell disease or functional asplenia should continue to receive antibiotic prophylaxis regardless of whether or not they received pneumococcal vaccines.

#### 33.4.1.2 Chlamydia trachomatis

Approximately 50–75% of infants born to *Chlamydia trachomatis*-infected mothers will become infected at one or more anatomical sites, including the conjunctiva, nasopharynx, rectum, and vagina. About 30% of infants with nasopharyngeal infections will develop pneumonia. The infants usually present at about 2–12 weeks of age with staccato cough and congestion but an absence



◘ **Fig. 33.2** Chest radiograph of 3-year-old female with *Streptococcus pneumoniae* pneumonia. Note the combination of consolidation and effusion affecting the right lung. (Image provided courtesy of FA Maffei)

of fever. The cough often interferes with the ability to feed. Infants generally have tachypnea and crackles on examination and the chest x-ray frequently shows hyperinflation. A peripheral eosinophilia may be present. Diagnosis can be made through culture or nucleic acid amplification tests. *C. trachomatis* is susceptible to macrolides, tetracyclines, quinolones, and sulfonamides. Erythromycin for 14 days is the treatment of choice for neonatal pneumonia.

#### 33.4.1.3 Chlamydia pneumoniae and Mycoplasma pneumoniae

*Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have an increased prevalence in older children.

*Mycoplasma pneumoniae* and *Chlamydia pneumoniae* play a greater role in causing respiratory tract disease in children than previously thought. An indolent course that develops over 5–7 days manifested by low-grade fever, sore throat, aches, and headaches characterizes both pathogens. After a few days, crackles may be heard, particularly in the bases where the infiltrates tend to occur. These organisms have been associated with the initiation, promotion, and exacerbation of asthma in children. In addition, a pertussis-like illness with acute bronchitis has been described. The CDC Epic Study showed that *Mycoplasma pneumoniae* was identified in 8% of children admitted to the hospital for community-acquired pneumonia. They also demonstrated that the detection of *Mycoplasma pneumoniae* increased gradually throughout the fall and peaked in the winter. Classic atypical pneumonias caused by these organisms are usually mild and self-limited. However, a number of studies have suggested that severe pulmonary infection may occur in otherwise healthy children. Pleural effusions occurred in 26% of children in the CDC Epic Study. Pneumatoceles, lung abscesses, pneumothoraces, bronchiectasis, chronic interstitial fibrosis, and acute respiratory distress syndrome, although rare complications, have all been reported. Serological testing is the most common means of diagnosis, but this is often retrospective. There are many tests available including culture, cold agglutinin antibodies, serology, and PCR assays. Treatment with antibiotics reduces the rate of recurrent wheezing episodes, decreases morbidity, and shortens the duration of symptoms. The organisms are susceptible to tetracyclines, macrolides, and quinolones. The 2011 Infectious Disease Society of America (IDSA) Guideline for Management of Community Acquired Pneumonia in Infants and Children recommends treatment with a macrolide whenever there is suspicion for *Mycoplasma pneumoniae* infection. There is evidence of emerging resistance to macrolides with a rate of 4% in the United States. Persistent fever 48 h after initiation of therapy may indicate macrolide resistance, and a tetracycline or fluoroquinolone is the drug of choice in these situations.



#### 33.4.1.4 Staphylococcus aureus

While *Staphylococcus aureus* pneumonia is uncommon, effusions ultimately develop in about 75% of cases, and pneumatoceles occur in 45–60%.

*Staphylococcus aureus* is a Gram-positive organism that can be found on the skin, nasal mucosa, and other mucus membranes. About 20–30% of children are carriers. It is generally spread by direct contact or by respiratory particles. *S. aureus* is an unusual cause of lower airway disease in otherwise healthy children (only 1% of children admitted to the hospital with community-acquired pneumonia were found to have *S. aureus* in the CDC Epic Study). It is more typically isolated from infants and young children with debilitating conditions. Primary *S. aureus* pneumonia presents in the winter or early spring with a short febrile prodrome and a rapid onset of pulmonary symptoms. Blood cultures are positive in 20–30% of patients. Secondary staphylococcal pneumonia will have a more prolonged prodrome with no seasonal predilection, but is often seen after influenza infections; in this setting, blood cultures are positive in about 90% of patients. Unilateral lobar disease is more typical with primary disease, while diffuse bilateral infiltrates are more frequent with secondary

pneumonia. Effusions can be diagnosed in about 15% of children at presentation but ultimately will develop in about 75% of cases. Pneumatoceles occur in up to 45–65% of children. Treatment is with cefazolin or oxacillin, but more organisms are becoming resistant and require therapy for serious or invasive disease with vancomycin, clindamycin, or linezolid.

Methicillin-resistant *Staphylococcus aureus* (MRSA) was once considered to be restricted to hospitals and long-term care facilities. However, community-acquired MRSA (CA-MRSA) is now a significant cause of a variety of infections (including pneumonia) in children without prior healthcare facility exposure. The majority of community-acquired MRSA infections involve minor skin and soft tissue infections, but invasive and sometimes fatal infections can occur in otherwise healthy individuals. CA-MRSA and healthcare-associated MRSA (HA-MRSA) can be distinguished by several important features. Patients with CA-MRSA by definition have not had recent hospitalization (acute or chronic care), prolonged antibiotic use, or chronic underlying disease. Toxin production also distinguishes CA-MRSA from HA-MRSA. Panton valentine leukocidin (PVL) is a toxin that is present in most CA-MRSA isolates but rarely in HA-MRSA isolates. PVL toxin lyses white blood cells leading to leukopenia and a decreased ability to kill *S. aureus*. Its production has been implicated as a contributor to the development of CA-MRSA necrotizing pneumonia. CA-MRSA isolates, unlike HA-MRSA, lack multidrug resistance. Thus, CA-MRSA is generally more susceptible to clindamycin, trimethoprim-sulfamethoxazole, and doxycycline than HA-MRSA, probably because HA-MRSA has developed resistance to survive in the healthcare setting.

#### 33.4.1.5 Group A Beta-hemolytic *Streptococcus*

*Group A beta-hemolytic Streptococcus* (GABHS) is a Gram-positive organism responsible for about 15% of pharyngitis and tonsillitis in children. It is rare as a primary cause of pneumonia (1% in the CDC Epic Study). When it does occur, the children generally have high fever and appear toxic. The pneumonia is typically lobar. Associated empyemas are common and pneumatoceles may develop. There are several virulent toxin-producing GABHS M-serotypes that are associated with toxic shock syndrome. An associated pneumonia occurs in 10–20% of children with toxic shock syndrome. GABHS are highly susceptible to penicillins and cephalosporins. In cases of toxic shock, clindamycin is often added to inhibit the production of streptococcal pyrogenic exotoxins A (SPE-A) and B (SPE-B).

#### 33.4.1.6 Group B *Streptococcus*

Early-onset disease (symptoms usually occur within 24 h of birth but can present within 6 days of birth) usually presents as sepsis, meningitis, or pneumonia. About 10% of infants with early-onset GBS will have pneumonia. Radiographic findings can be difficult to distinguish from hyaline membrane disease. The infant usually has systemic disease and blood cultures are frequently positive. Late-onset GBS usually occurs at 4–5 weeks of age and is predominantly caused by the type III serotype. In these infants, the infection is usually manifest as bacteremia without a focus or with meningitis; pneumonia is rare in late-onset disease. GBS is uniformly sensitive to penicillin.

#### 33.4.1.7 Bordetella pertussis

Pertussis or "whooping cough" is a highly contagious respiratory tract infection caused by the Gram-negative pleomorphic bacillus *Bordetella pertussis* and less commonly *Bordetella parapertussis*. With the development and wide-

spread use of a vaccine in the 1940s, a significant and sustained decrease in incidence has occurred. There has been a slight increase in pertussis cases reported to the CDC in recent years with almost 18,000 reported in 2016. Under-immunized or unimmunized infants are the most vulnerable. Nearly all deaths reported from pertussis occur in infants younger than 3 months of age.

Pertussis is often divided into catarrhal (fever, rhinorrhea, and initiation of cough), paroxysmal (severe coughing episodes, lymphocytosis, potential for complications), and convalescent stages (slow waning of cough over weeks to months). Complications include secondary bacterial or viral pneumonia, apnea, malnutrition, pulmonary hypertension, and neurologic involvement including seizures and encephalopathy. Infants less than 6 months of age are at highest risk for morbidity and mortality. Characteristic paroxysms of cough with an end-inspiratory whoop occur in children. Infants may present with a nonspecific cough with associated apnea and cyanosis, without a whoop. Adolescents may be asymptomatic or have only a mild prolonged cough. An increased white blood cell count up to 100,000/μL with a lymphocytosis is characteristic early in the course of the disease. The preferred test for laboratory confirmation is the detection of *B. pertussis* DNA by PCR assay. Bacteriologic culture provides a definitive diagnosis.

If administered during the early stages of the disease (first 7–10 days of illness), erythromycin for 14 days may decrease symptoms and reduce the risk of spread. A 5-day course of azithromycin or a 7–10-day course of clarithromycin has been found to be as effective with less gastrointestinal symptoms than observed with erythromycin. Corticosteroids, bronchodilators, or intravenous immunoglobulins have not demonstrated efficacy. Supportive care with supplemental oxygen, mechanical ventilation, intravenous fluids, maintenance of adequate caloric intake, and treatment of secondary bacterial infections are the mainstay of therapy. The use of extracorporeal membrane oxygenation in infants with hypoxemia, pulmonary hypertension, and right heart failure refractory to conventional mechanical ventilation has resulted in poorer outcomes than expected. Vaccination is preventative.



### 33.4.2 Viral Pneumonia

Approximately 70–80% of pneumonias in children are caused by viruses. There is considerable evidence that viral infections often precede bacterial pneumonias causing weakening of the host defenses. Viral pneumonias with RSV and parainfluenza are discussed in more detail in the bronchiolitis section.

#### 33.4.2.1 Influenza

Although death from influenza pneumonia is uncommon, a significant number of the children who died were previously healthy.

Influenza is the main viral cause of pneumonia in school-aged children requiring hospitalization. Annually, 870,000 children less than 5 years of age are hospitalized due to influenza. There are three serotypes, A, B, and C, which are further divided into subtypes based on the hemagglutinin and neuraminidase genes. Hemagglutinin 1, 2, and 3 and neuraminidase 1 and 2 typically infect humans. The gene segments for the surface glycoproteins are unstable. Only a few amino acid changes at critical sites regularly cause antigenic drift and a variant that is not recognized by antibodies acquired from previous infections or vaccines. In addition, genetic reassortment can occur via the exchange of entire gene segments when two different influenza viruses infect and replicate in the same host. This is frequently seen in aquatic birds, which are the main reservoir for influenza A, and in pigs that are susceptible to both avian and human influenza A viruses. Epidemics occur annually during the winter months with a short (1–3 days) incubation period. Devastating pandemics

have occurred in 1918, 1957, 1968, and 2009. The virus causes destruction of the ciliated respiratory epithelium within 1 day of symptoms. Airway edema and infiltration with inflammatory cells into the airway mucosa and epithelium follows. Slow repair occurs over 2–4 weeks. A severe fulminating pneumonia may result in hemorrhagic exudates that contain many polymorphonuclear and mononuclear cells. Destruction of the respiratory epithelium often leads to secondary bacterial infections.

In the 2017–2018 influenza season, 179 influenza-related pediatric deaths occurred; 43% were in otherwise healthy children, 26.2% had asthma or reactive airway disease, 16.8% had neurological disorders, and 10.5% were obese. Historically, 80–85% of pediatric deaths are in unvaccinated children 6 months and older. Rare complications of influenza include acute myositis, rhabdomyolysis, myocarditis, pericarditis, Reye syndrome, encephalitis, transverse myelitis, and Guillain-Barré syndrome.

Children may present with an abrupt onset manifested by high fever, myalgias, headaches, scratchy sore throats, and dry cough that generally lasts 4–7 days. Peripheral white blood counts are usually less than 5000/μL. Pulmonary infiltrates often involve multiple lobes. Bacterial coinfection, especially with MRSA, increases morbidity and mortality significantly.

Antiviral treatment with neuraminidase inhibitors, especially when given early, can reduce the severity and duration of symptoms. Children treated with oral oseltamivir within 48 h of symptom onset had a 36-h decrease in duration of illness, with greatest benefit in those receiving treatment within 24 h. However, no significant reduction in duration of illness was observed in children with asthma, despite improvement in pulmonary function as measured by forced expiratory volume at 1 s. Retrospective studies have observed a shorter hospital stay for children treated with oseltamivir. Zanamivir is a dry powder aerosol that must be delivered by a special breath-activated device; it should not be delivered via nebulizers, ventilators, or other aerosolized delivery devices. Children treated with zanamivir had a 1.3-day reduced median duration of illness. Zanamivir may increase the risk for bronchospasm and should generally be avoided in children with asthma or chronic lung disease. Intravenous peramivir was FDA approved in 2017 for uncomplicated influenza in children at least 2 years old who cannot tolerate oral oseltamivir or inhaled zanamivir. Studies of hospitalized pediatric patients are ongoing. Intravenous zanamivir will likely be made available if a newly emergent oseltamivir- or peramivir-resistant virus were to become a serious concern. Treatment with oseltamivir is recommended and has shown some benefit for children with serious, complicated, or progressive disease with proven or presumed influenza regardless of immunization status or onset of symptoms greater than 48 h. Amantadine and rimantadine are no longer recommended for treatment or prophylaxis due to the high rate of resistance of influenza A viruses.

In an observational study of 840 critically ill children, treatment with high-dose corticosteroids was associated with a higher risk of death. There is insufficient data to support treatment with immunoglobulin, although this is an area of active research. Aspirin or aspirin-containing products should be avoided due to the risk of Reye syndrome.

Immunoprophylaxis is the most effective strategy for the prevention of influenza infection. Inactivated vaccines have efficacy rates from 30 to 60%. Currently, the inactivated vaccine, trivalent or quadrivalent, is recommended annually for all children older than 6 months of age. The live attenuated intranasal vaccine can be an option for children older than 2 years of age without underlying chronic medical conditions if they refuse to receive the inactivated vaccine. However, evidence suggests that this vaccine is less effective.

Although antiviral medications may attenuate the course of influenza when given early, immunoprophylaxis with vaccines is the most effective strategy for the control of influenza infections.

Avian influenza has occurred in epidemics among persons with close contact to live, infected poultry. All children with pneumonia who progressed to ARDS succumbed to the disease.

#### 33.4.2.2 Avian Influenza

Avian influenza viruses do not normally infect species other than birds and pigs. However, in 1997, the first human death from avian influenza occurred in Hong Kong in a 3-year-old with Reye syndrome. Subsequently, an epidemic occurred among humans in Hong Kong with close contact to live, infected poultry. A highly pathogenic H5N1 subtype was isolated. This outbreak was curtailed by the culling of poultry with periodic closings of live bird markets for cleaning. In 2003 re-emergence of the avian H5N1 strain occurred. Through migrating birds, the virus rapidly spread to other countries in Southeast Asia and other parts of the world, including Africa and Europe. As of 2018, 856 human cases have been reported to WHO, with a 52.8% reported mortality. There are only a few proven human-to-human transmissions. Children uniformly present with fever and cough. Symptoms range from typical influenza-like symptoms to conjunctivitis to respiratory disease and failure. Significant laboratory data include leukopenia and thrombocytopenia. All children who developed pneumonia and progressed to ARDS died. Diagnosis remains difficult, as no tests are widely available.

#### 33.4.2.3 Novel H1N1 Influenza A

In April 2009, the Centers for Disease Control confirmed the emergence of a novel influenza A (H1N1) virus with genes from swine viruses of the Eurasian lineage and genes from avian influenza viruses. By June 2009, the first influenza pandemic since 1968 was declared, affecting over 191 countries and territories. In comparison to illnesses with seasonal influenza, the majority of cases occurred in individuals younger than 65 years of age, with nearly half of the cases occurring in children under 18 years of age. Fortunately, the pandemic was less severe than expected and comparable to an average influenza season.

The clinical symptoms can be typical for influenza: fever, sore throat, cough, and muscle aches with the addition of vomiting and diarrhea in children. A wide range of complications were reported ranging from mild-to-moderate (otitis media, sinusitis, myositis, and febrile seizures) to more severe complications, such as myocarditis, rhabdomyolysis, or encephalitis. Severe complications may frequently involve invasive bacterial coinfection (e.g., MRSA) and/or exacerbation of underlying medical conditions in particular asthma. Children who present initially with uncomplicated influenza may have rapidly progressive hypoxemic respiratory failure and multiorgan system dysfunction that is refractory to all therapies (◘ Fig. 33.3).

Of reported H1N1 deaths, approximately 20% were in children. The majority of these children had comorbid asthma, neurodevelopmental conditions, or obesity. An American Academy of Pediatrics Work Group identified children at greatest risk for life-threatening H1N1 influenza disease (► Box 33.1).

Like other strains of influenza, the Center for Disease Control recommended prompt empiric antiviral therapy with oseltamivir for infants, children, and adolescents of any age presenting with suspected or confirmed H1N1 influenza requiring hospitalization, especially with severe, progressive, or complicated illness regardless of length of time from presentation. See above for more details regarding antiviral therapy options. The current trivalent and quadrivalent vaccines now include newer variants of the 2009 H1N1 strain.

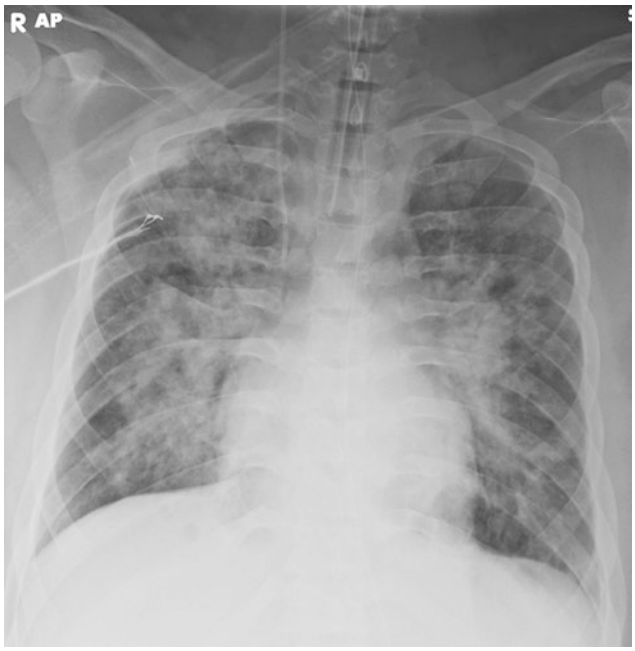



**Fig. 33.3** Chest radiograph of a 17-year-old with rapidly progressing hypoxemic respiratory failure secondary to H1N1. (Image provided courtesy of FA Maffei)

**Box 33.1 High-Risk Conditions Associated with Life-Threatening H1N1 Infection**

1. Neurological disorders, such as epilepsy, cerebral palsy, developmental delay, and neuromuscular disorders
2. Chronic respiratory diseases associated with impaired pulmonary function and/or difficulty handling lung secretions, moderate and especially severe persistent asthma, or technology-dependent children (e.g., those requiring oxygen, tracheostomy, or a ventilator)
3. Primary immunodeficiencies or conditions that require medications or treatments that result in secondary immunodeficiencies
4. Congenital heart disease
5. Metabolic (e.g., mitochondrial) or endocrine disorders, especially if cardiopulmonary function is impaired

Adapted from ► http://www.aap.org/new/swineflu.htm

### 33.4.2.4 Adenovirus

Adenoviruses have been implicated in 4–10% of pneumonias in children. Adenovirus infections peak between 6 months and 5 years of age. Adenoviruses are grouped into seven species, A through G. Species B, C, and E infect the upper and lower respiratory tracts. Respiratory infection with human adenoviruses is generally mild and self-limited in immunocompetent children. However, there are yearly outbreaks that cause severe respiratory infections and pneu-

Mortality from disseminated adenovirus infections remains high because of multiple organ system involvement.

monia, rarely progressing to ARDS. Outbreaks are generally seen in closed population clusters as in military installations, long-term care facilities and hospitals, and schools and college dorms. Disseminated infections usually occur in immunocompromised patients, especially patients following hematopoietic stem cell transplant or solid organ transplantation. Treatment of disseminated infections is mainly supportive, with mortality rates of 27–45% as the disease often involves multiple organ systems. Cidofovir (CDV) has reportedly reduced viral load and, in some series, improved survival in transplant patients. However, its use is also associated with significant toxicity. Brincidofovir (BCV) is a lipid formulation of CDV with improved oral bioavailability and favorable toxicity profile; however, studies have only shown modest benefit. Immunotherapy research has shown promising results. Survivors may have permanent lung injury often in the form of bronchiolitis obliterans. A live, oral vaccine for adenovirus types IV and VII is approved for use in military populations ages 17 through 50.

#### 33.4.2.5 Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

SARS and MERS rarely affect children, and when it does, morbidity is less, with rare mortality among children with comorbidities.



In 2003 and 2012, two human coronaviruses causing an acute respiratory syndrome emerged. SARS-CoV was first identified in China and is believed to be transmitted to humans from civets that were likely infected from the Chinese horseshoe bat. SARS quickly spread to 29 additional countries causing an atypical pneumonia with 8098 confirmed cases and 774 deaths. The epidemic was contained in 2004 following a highly effective public health response. MERS emerged in the Kingdom of Saudi Arabia. It is hypothesized that bats are the natural reservoir with camels and goats serving as intermediate hosts. MERS has spread to 27 additional countries with 2080 confirmed cases and 722 deaths as of 2017. Human-to-human transmission has been associated with healthcare workers and close contacts of infected persons. Adults (median age 40–50 years) have been mainly infected. Children less than 18 years of age accounted for approximately 5% of those affected with SARS, with a mean age of 12 years. No deaths were reported among children in the 2003 outbreak. In 2014, only 14 of the 701 confirmed cases (2%) were in children. The mean age was 99 months. Nine of these patients were asymptomatic and diagnosed during screening of family contacts; all were healthy. Three children developed mild respiratory symptoms. Two patients with comorbidities developed severe respiratory symptoms and multiorgan dysfunction and died. Following a mean incubation time of 5 days, symptoms developed including fever, chills, cough (occasionally bloody), shortness of breath, myalgia, headache, nausea, vomiting, diarrhea, sore throat, and malaise. Progression to severe disease was more rapid with MERS as compared to SARS, with 7 and 11 days, respectively. Laboratory abnormalities include elevated lactate dehydrogenase and liver enzymes, lymphopenia, and leukopenia. Radiographs of the chest show nonspecific infiltrates. Secondary bacterial infections have occurred. No approved therapeutics are available with clinical management primarily supportive.

#### 33.4.2.6 Hantavirus Cardiopulmonary Syndrome (HCPS)

Hantavirus is rare in infants and school-aged children. No deaths have been reported in children less than 14 years of age.

Hantavirus cardiopulmonary syndrome is a viral zoonotic disease that affects healthy children and adolescents who are exposed to aerosols of rodent excreta. The deer mouse is the main rodent reservoir. Most cases occur in the southwestern United States, but cases have been confirmed in 30 states. HCPS presents with a prodrome of fever, chills, myalgia, headache, and gastrointestinal symptoms. Respiratory compromise requiring supplemental oxygen generally

occurs within 72 h. The disease can progress to acute respiratory distress syndrome. The majority of deaths result from hypoxemia and cardiac dysfunction with marked hypotension and ventricular arrhythmias. In adults, the case fatality rate is approximately 38%. A case series of 13 children aged 10–16 years revealed that 92% of infected children developed HCPS, 33% died, and 67% were critically ill and required mechanical ventilation. Treatment is supportive. Extracorporeal membrane oxygenation was used on two patients, one of whom survived. Laboratory evaluation reveals thrombocytopenia, leukocytosis, and circulating immunoblasts. An elevated prothrombin time of ≥14 s is predictive of severe disease. No deaths were reported in children younger than 14 years of age. Diagnosis can be made by detection of hantavirus-specific immunoglobulin M, hantavirus-specific RNA by polymerase chain reaction, or hantavirus antigen by immunohistochemistry.

### 33.4.3 Pneumonia in the Immunocompromised Host

Respiratory infections in children with primary or acquired immunodeficiencies requiring intensive care are not uncommon. These infants and children are susceptible to many organisms that are rarely pathogenic in a normal host. Primary immunodeficiencies include abnormalities or deficiencies in immunoglobulins, T and B cells, phagocytes, natural killer cells, and complement. Acquired immunodeficiencies include asplenia, human immunodeficiency virus (HIV) infection, corticosteroid therapy, and immunosuppression used for marrow or solid organ transplants.

Immunocompromised children can present with attenuated signs and symptoms of respiratory infections. In addition to physical examination and chest radiographs, these children often require chest computed tomography to better delineate the extent of disease. Bronchoalveolar lavage, needle aspiration, or lung biopsies might be required to make a definitive diagnosis. Pulmonary specimens should be tested for common bacteria as well as for *Pneumocystis jirovecii*, acid-fast bacilli, *Nocardia*, *Legionella*, *Cryptococcus*, *Aspergillus*, *Candida*, *Histoplasma*, *Coccidioides*, and *Blastomyces*. Viruses such as cytomegalovirus, varicella, herpesvirus, and measles should be considered.

#### 33.4.3.1 *Pneumocystis jirovecii* Pneumonia (PJP)

*Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) is an opportunistic pulmonary pathogen in infants and children with human immunodeficiency virus (HIV) and other primary immunodeficiencies and hematological malignancies, solid organ and bone marrow transplant recipients, and patients on high-dose corticosteroid therapy for inflammatory and collagen-vascular diseases. It is a unicellular organism that exists as a cyst (the diagnostic form). The organism attaches to the type I alveolar cells resulting in an alveolitis characterized by ventilation-perfusion mismatch and decreased pulmonary compliance. If untreated, PCP carries a mortality rate of 25–50% and nearly 100% in the HIV-seropositive child. Fortunately, the incidence has markedly decreased with the administration of chemoprophylactic agents to high-risk patients. Children typically present with fever, tachypnea, nonproductive cough, and hypoxemia with an absence of crackles on auscultation of the chest. Lactate dehydrogenase levels are generally elevated. Bilateral diffuse alveolar infiltrates are seen with initial hilar involvement subsequently spreading to the periphery (◘ Fig. 33.4). Diagnosis is made by demonstrating the organism with dye-based staining in pulmonary tissue, respiratory secretions, or lung fluid or via PCR-based assays. Bronchoalveolar lavage is the most widely used technique to obtain lung fluid

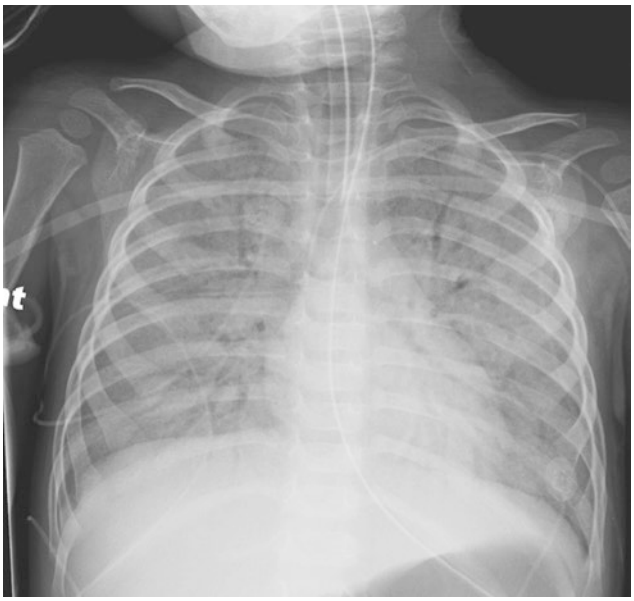


**Fig. 33.4** Chest radiograph of severe *Pneumocystis jirovecii* pneumonia in a 13-month-old male with combined immunodeficiency. Note the diffuse alveolar involvement and air bronchograms. (Image provided courtesy of FA Maffei)



for diagnosis. Treatment consists of supportive therapy with supplemental oxygen; ultimately continuous positive airway pressure or mechanical ventilation may be necessary if respiratory failure occurs. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended initial treatment. In patients who cannot tolerate TMP-SMX, then pentamidine isethionate should be used. Corticosteroids in anti-inflammatory doses as an adjunct to antimicrobial therapy have improved clinical outcomes. Concurrent pulmonary infections were found in 35% of patients, most frequently bacterial or cytomegalovirus pneumonia.

## 33.5 Diagnosis of Pneumonia

Determination of the etiologic agent in pneumonia is difficult. Fortunately, in most community-acquired pneumonias, identification of the specific causative organism is not critical. However, in children with a complicated course that fails to respond to standard therapies, definitive diagnosis of the etiologic agent is essential. Complete blood counts, inflammatory markers, and chest radiographs do not differentiate the causative agents for pneumonia. Blood cultures are rarely positive outside of the neonatal period with recent studies demonstrating rates of 1.4–3.4%. Despite these low rates, it is still recommended that children admitted for CAP should have blood cultures sent. PCR for diagnosis of respiratory pathogens has become common, and there is some evidence that these tests decrease antibiotic usage as well as chest radiographs. In addition to PCR, rapid antigen tests are available for RSV, rhino−/enterovirus, parainfluenza, influenza, and adenovirus. Nasopharyngeal swabs for viral cultures generally take 7–8 days to become positive, and in one study, 86% of the patients had been discharged prior to the positive results. Older children and adolescents might be able to produce sputum for Gram stain and culture. An adequate specimen should contain more than 25 leukocytes and fewer than 25 squamous epithelial cells per low-power field. In the intubated patient, a

tracheal aspirate can be more easily acquired. However, interpretation of the results of Gram stains and cultures is at times difficult in differentiating colonizing from pathologic organisms. Colonization of the endotracheal tube may occur as early as 12 h but most frequently between 60 and 96 h. The oropharynx becomes colonized within 36 h, the stomach at 36–60 h, and the lower respiratory tract between 60 and 84 h. In addition, a comparison of infectious agents isolated by both tracheal aspirates and bronchoalveolar lavage found only 36% concordance.

Bronchoalveolar lavage (BAL) can be safely used to obtain secretions from the lower airways for Gram stain and culture. It is especially useful in the diagnosis of pneumonia in the immunocompromised child. However, BAL performed directly through the bronchoscope carries a risk of contamination. Non-bronchoscopic double-lumen plugged catheters can be inserted blindly through the endotracheal tube to obtain a specimen. A recent study in 25 patients demonstrated that when the results of blind tracheal aspirate and BAL were compared, only 36% of patients demonstrated the same organisms by both techniques. Transthoracic needle aspirations are performed in some centers with good results. One study reported a diagnostic success rate in 59% of patients. The incidence of pneumothorax was approximately 20%, but none required subsequent placement of a pleural drainage catheter. A lung biopsy is rarely needed to make a definitive diagnosis.

All patients admitted to the hospital for CAP should have a chest radiograph done to describe parenchymal infiltrates and identify complications of pneumonia such as parapneumonic effusion. Routine daily chest radiographs are not recommended; however, if patients fail to improve after 48 h of antibiotics treatments, repeat chest radiography is indicated. If the presence of pleural fluid is not clear on chest radiograph, then chest CT or bedside ultrasound (US) should be considered. Chest US is considered safer due to the lack of ionizing radiation. In addition, US can help to identify simple vs. loculated effusions which may affect treatment decisions.

## 33.6 Treatment

Supportive treatments with oxygen and intravenous fluids are often standard therapies. As both pneumonia and mechanical ventilation can cause an elevation in antidiuretic hormone levels, careful fluid monitoring is essential to avoid overhydration, excessive lung water, and hyponatremia. Initial antibiotic choices should be empiric and based upon the likely organisms for each age group because of the difficulty in identifying the causative agent. Empiric antibiotics for patients requiring hospital admission were recommended in the 2011 IDSA Guideline for Management of Community Acquired Pneumonia in Infants and Children (■ Table 33.3).

The child's respiratory status including respiratory rate, work of breathing, pulse oximetry, and central nervous system response should be closely monitored. There are several options available for noninvasive respiratory support. High-flow nasal cannula provides heated and humidified air blended with oxygen through a nasal cannula at rates up to 8–10 L/min in infants and 60 L/min in children and adults. This is thought to provide some positive airway pressure, maintain a constant delivered $FiO_2$, wash out $CO_2$ from anatomical dead space, improve mucociliary clearance due to humidification, and decrease patients' work of breathing. There is a paucity of data around the use of high-flow nasal cannula in children with community-acquired pneumonia. A recent

**Table 33.3** Antibiotic regimen for community-acquired pneumonia

| Inpatient All ages | Presumed bacterial infection | Presumed atypical pneumonia | Presumed influenza pneumonia |
|---|---|---|---|
| Fully immunized; local penicillin resistance in invasive strains of pneumococcus is minimal | Ampicillin or penicillin G; alternatives, ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA | Azithromycin; alternatives, clarithromycin, erythromycin, doxycycline, or levofloxacin (for children who have reached growth maturity and cannot tolerate macrolides) | Oseltamivir or zanamivir |
| Not fully immunized; local penicillin resistance in invasive strains of pneumococcus is significant | Ceftriaxone or cefotaxime; alternative, levofloxacin; addition of vancomycin or clindamycin for suspected CA-MRSA | As above | As above |

Adapted from Bradley (2011)



multicenter RCT demonstrated that among infants with bronchiolitis, those treated with high-flow nasal cannula had significantly lower rates of escalation of care due to treatment failure with no difference in length of stay or duration of oxygen therapy.

Noninvasive BiPAP ventilation can be effective for children with moderate respiratory insufficiency.

Another option for noninvasive respiratory support is bi-level positive airway pressure (BiPAP). BiPAP decreases patients' work of breathing and recruits alveoli resulting in decreased V/Q mismatch. It was effective in children with mild-to-moderate respiratory insufficiency, defined as an A-a gradient >100 and <250 mm Hg or $PaO_2/FiO_2$ ratio < 200 but >100. There are many options for masks to use with BiPAP including nasal pillows, nasal masks, masks covering the nose and mouth, and full-face masks. Serial evaluation of mask-face contact areas is essential to avoid skin breakdown. Often older children tolerate BiPAP initiation with minimal coaching; however, younger children may require sedation to limit anxiety or agitation with BiPAP.

Children with moderate or severe respiratory insufficiency often require intubation and mechanical ventilation. Children with respiratory failure secondary to pneumonia often require increased positive end-expiratory pressure (PEEP), increased inspiratory time, and aggressive pulmonary toilet to recruit alveoli. For patients requiring high levels of PEEP, adequate sedation is often required to prevent patient/ventilator asynchrony and barotrauma. Spontaneous respirations should be encouraged while on mechanical ventilation, although some patients require the use of neuromuscular blockade to allow mechanical ventilation. Some patients with pneumonia progress to acute respiratory distress syndrome (ARDS). Please see ARDS chapter for definition and lung protective ventilation strategies.

Pneumonias can often be complicated by the development of pleural effusions and empyemas. These occur when the fluid production by the interstitial lung tissue exceeds the maximum pleural lymphatic flow. In addition, direct infection in the pleural space contributes to fluid accumulation and may obstruct lymphatic drainage through the inflammatory response. Parapneumonic effusions often occur from pneumonia as white blood cells and other infectious debris block the lymphatics resulting in elevation of protein in the pleural space, which increases pleural fluid colloid osmotic pressure, and consequent failure of fluid reabsorption. On physical exam, the child has decreased breath sounds over the effusion. In older children, auscultatory percussion changes might be appreciated. Plain chest radiographs can reveal most clinically significant effusions. Ultrasound and chest computed tomograms are useful in determining the volume and quality of the fluid and the presence of loculations. Simple parapneumonic effusions or transudates can also be differentiated from exudates by using the criteria of Light et al. (▶ Box 33.2). The Light criteria misclassify about 25% of transudates as exudates usually in patients receiving diuretics. In these patients, a serum to pleural fluid gradient greater than 3.1 gm/dL is consistent with a transudate. A pleural fluid pH less than 7.2 indicates a complicated effusion that is likely exudative and requires drainage, whereas a pleural fluid pH more than 7.3 suggests that the effusion may be managed with systemic antibiotics alone.

Complicated parapneumonic effusions or empyemas occur when the fluid becomes purulent. During this stage, the effusions undergo a fibrinopurulent stage with many polymorphonuclear leukocytes, bacteria, and cellular debris entering the fluid. Fibrin is deposited over the pleural surfaces and loculations begin to form. The pH and glucose levels fall as the LDH levels rise. If untreated, they often progress to a third organizing stage in which the exudate develops into an inelastic, fibrotic peel that restricts the lung.

Treatment for parapneumonic effusions, as recommended by the 2011 IDSA Guideline for Management of Community Acquired Pneumonia in Infants and Children, is recommended based on the size, degree of respiratory compromise, and whether the fluid is simple or loculated. Small effusions that don't cause a high degree of respiratory compromise may be amenable to treatment with antibiotics alone. Larger effusions that cause a high degree of respiratory compromise will likely require chest tube placement and drainage. Furthermore, loculated fluid collections are unlikely to improve with drainage alone, and both chest tube drainage with fibrinolytics and video-assisted thoracoscopic surgery (VATS) have been found to be effective treatment options. There is inadequate data to recommend one treatment over the other since both interventions have been shown to improve patient outcomes, including resolution of infection and decreased length of stay in comparison to conservative therapy. Fibrinolytic regimens used in children include both tissue plasminogen activator and urokinase. The risks for bleeding are reportedly low, but this therapy requires close monitoring of chest tube drainage. It is also contraindicated in patients with bronchopleural fistulas or in patients who won't tolerate chest tube clamping during instillation. Chest tube and fibrinolytic therapy was effective 80% of the time with similar length of stay and lower costs when compared with early VATS. There was a failure rate of 15–20% in which patients then need to proceed with VATS. VATS was shown in observational studies to have good outcomes in safety and efficacy.

**Box 33.2 Light Criteria with Individual Sensitivity and Specificity of Tests to Distinguish Exudative From Transudative Effusions**

- Pleural fluid may be classified as exudative, if one or more of the following criteria are met
- Pleural fluid protein divided by serum protein >0.5 (sensitivity 98%, specificity 83%)
- Pleural fluid lactate dehydrogenase (LDH) divided by serum LDH > 0.6 (sensitivity 86%, specificity 84%)
- Pleural fluid LDH is more than two-thirds of the upper limit of normal for serum LDH (sensitivity 82%, specificity 89%)

Adapted from Light (2002)

## 33.7 Conclusion

Acute pulmonary infections are common diagnoses that require admission to pediatric intensive care units. Understanding the pathophysiology of lower respiratory infections enables the intensivist to tailor therapy to the individual child and pathogen. Early establishment of a specific etiology and the selection of the correct treatment plan directly impacts clinical outcome.



### Review Questions

1. *A 3-month-old, former 27-week premature infant with bronchopulmonary dysplasia presents with clinical signs of bronchiolitis. Analysis of nasopharyngeal secretions by polymerase chain reaction testing identifies respiratory syncytial virus. Which of the following therapies have been proven to have a consistent benefit for RSV bronchiolitis?*
   A. Aminophylline
   B. Bronchodilators
   C. Corticosteroids
   D. Ribavirin
   E. Supportive care

2. *Palivizumab is indicated for which of the following children?*
   A. A 5-month-old, former 27-week premature infant who just underwent surgical repair of a large ventricular septal defect who received palivizumab 2 weeks ago
   B. A 9-month-old, former 28-week premature infant with mild bronchopulmonary dysplasia who received palivizumab 2 weeks ago
   C. A 1-month-old, former 36-week premature infant with peripheral pulmonic stenosis who has never received palivizumab
   D. A 2-month-old full-term infant with a urea cycle defect who has never received palivizumab
   E. An 8-month-old, former 25-week premature infant with bronchopulmonary dysplasia who received his fifth dose of palivizumab a month ago

3. *A 5-year-old, unimmunized male with moderately severe asthma requires hospital admission with a 12-h history of fever, cough, and myalgias in the middle of an influenza outbreak. The most appropriate initial management of this child includes which of the following?*
   A. Intravenous peramivir administered after confirming the diagnosis with rapid testing
   B. Intravenous zanamivir administered as soon as possible

C. Oral amantadine administered as soon as possible
D. Oral oseltamivir administered as soon as possible
E. Orally inhaled zanamivir administered after confirming the diagnosis with rapid testing

4. *A 7-year-old presents with a high fever, respiratory distress, and a parapneumonic effusion on chest radiograph. Which of the following findings would MOST likely suggest the need for video-assisted thoracoscopic surgical drainage of this effusion?*
   A. A mediastinal shift away from the effusion.
   B. A pleural fluid pH > 7.3 and glucose >200 mg/dL.
   C. Persistent drainage for more than 5 days from a percutaneously placed thoracentesis catheter.
   D. Less than one-fourth of the hemithorax is opacified on chest x-ray.
   E. The presence of loculations on ultrasound or computer tomography images.

5. *A 4-year-old male presents with acute hypoxemic respiratory failure ($PaO_2$/$FiO_2$ ratio = 150), disseminated intravascular coagulation, and renal insufficiency secondary to catecholamine-resistant shock. Rapid antigen testing identifies influenza. In addition to oral oseltamivir, the initial antimicrobial coverage should include which of the following?*
   A. Cefepime
   B. Intravenous immunoglobulin
   C. Intravenous zanamivir
   D. Trimethoprim-sulfamethoxazole
   E. Vancomycin

6. *A 16-year-old male presents with a 3-day history of fever, chills, myalgia, headache, and gastrointestinal symptoms. On clinical exam, he is febrile, tachypneic with scattered crackles, and hypotensive. There is no rash or evidence of animal bite on exam. His initial laboratory results are remarkable for thrombocytopenia, leukocytosis with an increased percentage of circulating immunoblasts, and elevated levels of lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase. His prothrombin time is 16 s. He is admitted and his respiratory status continues to deteriorate ultimately requiring mechanical ventilation. He remains in refractory shock for several days. After an extensive diagnostic work-up, he is diagnosed with hantavirus cardiopulmonary syndrome based on the detection of hantavirus-specific immunoglobulin M. Of the following, which is most likely to be part of his medical history?*
   A. An underlying immunodeficiency
   B. Being a member of the high school wrestling team
   C. Exposure to rodent excrement
   D. Intravenous drug use
   E. Residence in the Southeastern United States

7. *Corticosteroids have the MOST established benefit in which of the following clinical scenarios?*
   A. A 7-week-old infant with severe bronchiolitis secondary to respiratory syncytial virus.
   B. A 6-month-old, unimmunized infant with severe hypoxemia and respiratory failure secondary to pertussis
   C. A 14-year-old female with necrotizing pneumonia secondary to community-acquired methicillin-resistant *Staphylococcus aureus*

D. A 14-month-old with a history of acquired immunodeficiency syndrome and currently in hypoxemic respiratory failure secondary to *Pneumocystis jirovecii* pneumonia (previously called *Pneumocystis carinii* pneumonia)
E. A 16-year-old native American female with severe cardiopulmonary dysfunction secondary to a Hantavirus infection

**Answers**

1. E
2. A
3. D
4. E
5. E
6. C
7. D

## Suggested Readings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