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Introduction and Epidemiology

Globally, pneumonia is the leading cause of death in children under 5 years of age and accounts for 18% of deaths in this age group (Madhi et al., 2012). In the United States, there are approximately 2 million outpatient visits (Kronman et al., 2011) and over 100,000 pediatric hospitalizations annually for community-acquired pneumonia (CAP) (Jain et al., 2015). Among children’s hospitals in the United States, CAP accounts for the highest number of days of antibiotic use (Gerber et al., 2013) and is the second most costly reason for pediatric hospitalization (Keren, 2012). The annual incidence of pneumonia requiring hospitalization was found in one study to be 15.7 cases per 10,000 children and higher among children under 2 years of age (Jain et al., 2015). Despite its prevalence, pneumonia has varying definitions using both clinical and radiographic characteristics. A broad definition of pneumonia is an acute infection of the lower respiratory tract, which also overlaps with other entities such as bronchiolitis (Selwin, 1990). Other definitions are more specific and include “the presence of fever, acute respiratory symptoms, or both, plus evidence of parenchymal infiltrates on chest radiography” (McIntosh, 2002).

This article will address the pathophysiology of community-acquired pneumonia in the pediatric population, common pathogens by age, clinical presentation, differential diagnosis, diagnostic imaging and laboratory recommendations, indications for hospitalization, treatment guidelines and disease complications.
Pathophysiology

Viral Pneumonia

Viral pneumonias are the result of direct inoculation of the upper respiratory tract by the viral pathogen(s) from inhalation of infectious secretions or from fomites in the child’s environment. The virus travels distally to the lower respiratory tract, multiplies and causes de-epithelialization and inhibits ciliary function, resulting in mucus plugging and a build-up of debris in the airways. Once the virus spreads to the alveoli, cells break down causing loss of surfactant formation and subsequently the formation of hyaline membranes and possible pulmonary edema. Mononuclear cells infiltrate the submucosal and interstitial spaces, worsening edema and decreasing gas exchange across alveolar membranes (Shah and Bradley, 2019; Johnson et al., 2007). Obstruction of the bronchioles with mucus and cellular debris can, via a ball-valve mechanism, create air trapping and hyperinflation particularly with RSV pneumonia. This process can also cause segmental or subsegmental atelectasis and contribute to ventilation-perfusion mismatch and further hypoxemia (Shah and Bradley, 2019).

Multiple factors may predispose children to viral pneumonia with varying degrees of severity. Children with underlying pulmonary disease, including bronchopulmonary dysplasia or chronic lung disease, that results in difficulty clearing increased secretion volume can precipitate worsening bronchospasm and wheezing, atelectasis and hypoxemic respiratory failure. The small caliber of infant airways and the lack of pores of Kohn (the connections between alveolar spaces) can also result in atelectasis and wheezing, predisposing infants to more severe viral pneumonia. Finally, defects in the innate or humoral immunity critical for defense against viral pathogens may predispose to more severe viral pneumonia.

Bacterial Pneumonia

The lung’s defense mechanisms against bacterial pathogens include ciliated epithelium and mucus which serve to trap and remove organisms from the airways, alveolar macrophages which engulf and kill airway bacteria, the reticuloendothelial system which prevents hematogenous spread, and innate and specific humoral immunity that defuses infecting bacteria. If any of these barriers is disrupted, bacteria may enter the lung, proliferate, and begin cellular destruction resulting in pneumonia. The majority of bacterial pneumonias occur following nasopharyngeal colonization. This may follow a viral upper respiratory infection with de-epithelialization increasing the risk of bacterial colonization. A study of children with CAP compared to a healthy cohort demonstrated that children with CAP with more likely to have had recurrent respiratory infections, wheezing or otitis media prior to age two (Heiskanen-Kosma et al., 1997). Animal models have also demonstrated that viral respiratory infections often precede bacterial pneumonia (McCullers and Rehg, 2002; McCullers, 2014). Recent work has elucidated changes in the nasopharyngeal microbiome that contribute to lower respiratory tract infections. It is likely that a combination of microbiota and host factors contribute to pathogenic lower respiratory infections (Man et al., 2019; Kelly et al., 2017).

Streptococcus pneumoniae is the most common bacterial pathogen in pediatric pneumonia. Once colonized, bacteria may enter the lower respiratory tract via inhalation, aspiration, or less frequently via hematogenous spread. Pneumococci adhere to the bronchioles, multiply, and begin an alveolar inflammatory cascade with the release of exudative fluid. Fibrin is deposited and polymorphonuclear lymphocytes invade the alveoli, so called “red hepatization,” followed by increased macrophage activity, or “white hepatization.” Exudative fluid allows the bacteria to multiply and spread to adjacent alveoli contributing to the typical pattern of lobar pneumonia (Harford and Hara, 1950). When pneumonia is caused by more virulent pathogens such as S. aureus, there is increased tissue destruction and pulmonary abscesses and necrosis occur more commonly.

Atypical Pneumonia

Mycoplasma pneumoniae is a mucosal pathogen that is spread via aerosolized particles. Attachment of the bacteria leads to a cytokine response with both lymphocytes and neutrophils attracted to the mucosal cells and subsequent development of inflammatory infiltrates in the airways (Waites and Talkington, 2004). After Mycoplasma has attached to the respiratory epithelium, oxidative stress ensues leading to loss of function of the epithelium and sometimes necrosis (Almagor et al., 1983). The pattern of lung damage may include bronchiolar or alveolar edema or diffuse alveolar damage.

Causative Organisms

The introduction of the pneumococcal conjugate vaccine (PCV) in 2000 has changed the epidemiology of CAP and dramatically decreased the rates of invasive pneumococcal disease (Pilishvili et al., 2010). The PCV13 vaccine was introduced in 2011 and current CDC recommendations are for all children to receive the PCV13 vaccine at age 2, 4, 6 and 12–15 months (CDC, 2019a). In addition to the PCV13 vaccine, children with high risk conditions, including sickle cell disease, and others at risk of invasive pneumococcal disease should receive the pneumococcal polysaccharide vaccine (PPSV 23) after age 2 years (CDC, 2019a). The etiology of CAP varies by age with viral organisms predominating in younger children and bacterial causes increasing with age (Table 1 and Fig. 1). Certain comorbidities may predispose children to specific organisms. For example, children with sickle cell disease are at risk for infection with encapsulated organisms, such as S. pneumoniae. Children who are immunosuppressed may suffer from CAP due to commonly detected organisms but are also at risk for pneumonia due to more unusual
or fulminant pathogens, such as mycobacteria, *Pneumocystis jirovecii*, or fungi (Table 2). Commonly detected pathogens in the immunocompetent child will be reviewed here.

### Common Pathogens by Age

#### Neonates 0–28 Days

Any infant 28 days or younger with a temperature ≥ 38 °C requires a full evaluation for serious bacterial infections with blood, urine and cerebrospinal fluid (CSF) cultures due to the risk of invasive bacterial or viral (i.e., herpes simplex virus) disease in this age group. Neonates are at risk for perinatally-acquired congenital pneumonia due to ascending transmission of pathogens across the cho-
rioamniotic membranes or via hematogenous spread from the placenta, or early-onset pneumonia (during the first 7 days of life) due to exposure to maternal pathogens during birth (Hooven and Polin, 2017). Congenital pathogens include *Toxoplasma gondii*,

| Immunocompromised | Unimmunized | Sickle cell disease | Cystic fibrosis |
|-------------------|-------------|---------------------|-----------------|
| *Streptococcus pneumoniae* | *Streptococcus pneumoniae* | Encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae* type B) | *Haemophilus influenzae* type B |
| *Staphylococcus aureus* | *Bordetella pertussis* | *Staphylococcus aureus* | *Staphylococcus aureus* |
| *Pseudomonas aeruginosa* | *Haemophilus influenzae* type B | *Mycoplasma pneumoniae* | *Stenotrophomonas maltophilia* |
| Mycobacteria | Varicella | *Achromobacter xylosoxidans* | *Pseudomonas aeruginosa* |
| *Pneumocystis jirovecii* | *Rubeola* (measles) | *Varicella* | *Burkholderia cepacia* |
| Fungi (aspergillus) | | | Fungi (aspergillus) |

Table 1: Etiology of pneumonia in special circumstances.

Fig. 1 Viral and bacterial pathogens detected in hospitalized children with CAP in the United States in the CDC EPIC study. Panel A denotes the portion of patients with no pathogen detected, single bacterial pathogen, bacterial-viral coinfection and solitary viral pathogen based on age group. Panel B denotes the specific pathogen detected with darker shading indicating a single pathogen and lighter shading indicating the pathogen was detected with at least one other pathogen. Panel C denotes the proportion of pathogens detected by age group. Legend: *RSV*, respiratory syncytial virus; *HRV*, human rhinovirus; *HMPV*, human metapneumovirus; *AdV*, adenovirus; *PIV*, parainfluenza virus; *flu*, influenza A or B; *CoV*, coronavirus. Reproduced with permission from Jain S, Williams DJ, Arnold SR, et al. (2015) Community-acquired pneumonia requiring hospitalization among U.S. children. *New England Journal of Medicine* 372(9): 840. Fig. 2.
cytomegalovirus, *Treponema pallidum* (congenital syphilis) and herpes simplex virus (Hooven and Polin, 2017). Early-onset bacterial pneumonia pathogens include group B streptococcus, enteric gram-negative bacilli including *Escherichia coli* and *Klebsiella*, and *Listeria monocytogenes*. There is low risk of *Chlamydia trachomatis* infection in the developed world due to routine prenatal screening of pregnant women; however, this should be considered in the infant born to a mother with minimal prenatal care (Pelton and Hammerschlag, 2005). Risk factors to consider in the evaluation of an infant with potential early-onset pneumonia are the same as those for bacteremia and include chorioamnionitis, prematurity, low birth weight, prolonged rupture of membranes (>18 h), and maternal colonization with a known pathogen (e.g., group B streptococcus) (Hooven and Polin, 2017). Late-onset neonatal pneumonia (>7 days) may be caused by *Staphylococcus aureus*, *Enterobacter* species, *Escherichia coli*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* or lower respiratory tract viruses. Risk factors for late-onset neonatal pneumonia include prematurity, low birth weight, and duration of mechanical ventilation in the neonatal intensive care unit (Kawanishi et al., 2014).

### Infants and Toddlers 29 Days to 4 Years

Pneumonia in this age group is more often viral rather than bacterial, with the most commonly detected viruses including respiratory syncytial virus (RSV), human rhinovirus, human metapneumovirus (HMPV) and adenovirus (Jain et al., 2015). Over 25% of patients hospitalized in this age group have viral-viral coinfection (Jain et al., 2015). The most commonly detected bacterial cause of CAP in this age group is *Streptococcus pneumoniae*. In incompletely immunized and unimmunized children, *Haemophilus influenzae* type B and *Bordetella pertussis* must also be considered. *Mycoplasma pneumoniae* is less often a detected pathogen in the 29 days to 2 years age group compared to children over 2, and particularly those 5 years and older (Jain et al., 2015). In children 2–4 years of age, *Mycoplasma* is more common than *S. pneumoniae* (Jain et al., 2015).

### Children 5 Through 12 Years

Although viruses remain the most commonly detected cause of CAP in school-aged children, *Mycoplasma* is the most prominent detected bacterial pathogen (Jain et al., 2015; Marchello et al., 2016). *Chlamydophila pneumoniae* and *S. pneumoniae* are also isolated in this age group (Jain et al., 2015; Marchello et al., 2016). Children with prolonged cough, viral URI prodrome, or those with classic symptoms merit pertussis testing, as *Bordetella pertussis* has been isolated in up to 17% of these children (Marchello et al., 2016). Immunity from the pertussis vaccine decreases over time, so even immunized children remain at risk (Tartof et al., 2013). *S. aureus*, *Streptococcus* species, non-typeable *H. influenzae* are less common pathogens, but should be considered, particularly in children with drug-resistant or complicated pneumonias.

### Adolescents 13 Through 17 Years

Adolescents have similar etiologies of pneumonia as adults. Like all age groups excluding the neonatal population, viruses remain the most common cause of CAP, particularly human rhinovirus and influenza (Jain et al., 2015). *Mycoplasma* was the most commonly isolated pathogen in one study of hospitalized children in the United States, but there was a higher proportion of bacterial pneumonia overall, including *S. pneumoniae*, *S. aureus*, streptococcus, and *H. influenzae* (Jain et al., 2015).
Clinical Presentation

There is no universal presentation of pneumonia. Overlapping features occurring in various lower respiratory tract conditions (e.g., asthma, bronchiolitis, pneumonitis, pneumonia) makes the clinical diagnosis challenging. Common signs and symptoms include fever, cough, tachypnea, increased work of breathing, dehydration and hypoxia. Other symptoms can include abdominal pain and emesis. Physical exam findings may include rales, crackles, wheezing, dyspnea as demonstrated by retractions, nasal flaring or grunting, and decreased breath sounds.

Clinical prediction models incorporating both signs and symptoms tend to have better positive predictive values than any single finding, likely due to the heterogeneity of children presenting with pneumonia (Hirsch et al., 2019). An additional challenge is that clinical findings are not routinely agreed upon by clinicians. In one study, only three examination findings—wheeze, retractions and respiratory rate—had acceptable agreement between providers. Others, including cough, crackles, rhonchi, decreased breath sounds and capillary refill had poor to fair reliability and thus may be less useful in the prediction of pneumonia and evaluating the severity of disease (Florin et al., 2017). Given their subjectivity, auscultatory findings have not been shown to be strongly associated with a diagnosis of pneumonia on chest radiograph (Shah et al., 2017). Hypoxemia (≤96%) and increased work of breathing have been shown to have increased likelihood ratios for radiographic pneumonia (LR, 2.8 [95% CI, 2.1–3.6] and LR, 2.1 [95% CI, 1.6–2.7], respectively), while normal oxygen saturation (>96%) is a negative predictor for pneumonia (LR 0.47 [95% CI, 0.32–0.67]) (Shah et al., 2017). Afebrile children with wheezing are unlikely to have pneumonia, particularly if they are not hypoxic. Routine use of chest radiography in this group is thus not generally recommended (Mathews et al., 2009).

The definition and management of pneumonia varies based on clinical setting. In lower-middle income countries, where imaging may not be routinely available, the World Health Organization (WHO) defines pneumonia as cough, difficulty breathing, tachypnea or chest indrawing as having pneumonia and may be treated as outpatients. Children with these symptoms and an associated “general danger sign,” such as dehydration, are considered to have “severe pneumonia” and hospitalization is recommended (WHO, 2014). Regardless of setting, the signs of respiratory distress in children are a critical part of the evaluation. Signs of respiratory distress in children include age-specific tachypnea, dyspnea, chest indrawing or retractions, grunting, nasal flaring, apnea, altered mental status or sustained hypoxemia (oxygen saturation <90% in room air).

Differential Diagnosis

The differential diagnosis of pneumonia includes upper and lower respiratory tract infections, infectious and noninfectious pulmonary conditions, and cardiac and vascular anomalies. Formulating a differential diagnosis should rely on a focused history tailored to the age of the patient, their underlying comorbidities, and their physical examination.

History should focus on the duration and quality of cough (e.g., spasmodic, nocturnal, barking), presence of fever, history of a choking event, and any history of respiratory distress. Patient and family history of asthma or atopy is also important to differentiate asthma from pneumonia or to provide targeted therapies for reactive airways disease, if necessary. Sick contacts, immunization status (particularly influenza, pertussis, Haemophilus influenzae Type B and pneumococcal conjugate vaccines), recent travel, and any animal or environmental exposures can provide important diagnostic clues.

Cough is a frequent, non-specific symptom of pneumonia and has a broad differential diagnosis. Cough in infants when associated with poor weight gain, cyanosis, or sweating with feeds should prompt evaluation for a congenital cardiac lesion. Paroxysmal cough, cough with color change or apnea raises the suspicion for pertussis in infants. In older infants and toddlers (typically 6 months to 3 years of age), barking cough with fever and a hoarse cry or voice with or without inspiratory stridor should raise suspicion for croup. Lower respiratory tract findings are generally absent on exam. Recurrent barky cough or stridor should make the clinician consider an anatomic lesion, such as a vascular ring or sling, predisposing to compression of the trachea. Children with a history of a choking episode with subsequent cough, fever or focal findings on lung examination may have aspirated a foreign body. Focal wheezing may also accompany an aspiration event. Fever may be present in both upper and lower respiratory tract diseases and is not specific for pneumonia. Nocturnal cough, particularly when associated with wheezing or signs on exam of allergic rhinitis (allergic shiners, boggy nasal turbinates, cobblestoning of the oropharynx) is more typical of an allergic etiology or underlying reactive airway disease or asthma.

Abdominal pain and emesis have a broad differential in their own right, but pneumonia should be considered due to the ability for basilar pneumonias or effusions to irritate the T9 dermatome which is shared between the lungs and abdomen (Leung and Sigal, 2003). As such, a lower lobe pneumonia may mimic appendicitis, for example. Less common mimics of pneumonia include collagen vascular diseases (systemic lupus erythematosus, scleroderma, rheumatoid arthritis), congenital lung anomalies, malignancy, heart failure, pulmonary hemorrhage, sarcoïdosis, pulmonary embolus or environmental irritants.

In children with recurrent pneumonias, particularly those with uncommon pathogens identified, the clinician should consider underlying immunodeficiency (e.g., common variable immunodeficiency, chronic granulomatous disease), cystic fibrosis or congenital lung malformation. Cystic fibrosis should also be considered if there is associated failure to thrive, malabsorptive symptoms (greasy stools), severe constipation or intestinal obstruction or if there is a positive family history. Recurrent pneumonias within the same lobe should prompt investigation for an anatomic anomaly.
Special Causes

Beginning in June 2019, an outbreak of e-cigarette or vaping use associated lung injury (EVALI) was formally recognized by the Centers for Disease Control (CDC). In 2019, over 2000 cases of EVALI requiring hospital admission have been reported in the United States. (Centers for Disease Control and Prevention, 2019) 16% of patients with EVALI are younger than 18 years old (Centers for Disease Control and Prevention, 2019). EVALI can present with systemic symptoms such as fever and chills, symptoms of gastrointestinal distress and respiratory symptoms such as, cough, chest pain and shortness of breath, similar to pneumonia. All adolescents should be interviewed privately regarding any history of vaping or use of e-cigarettes and if positive, EVALI should be considered in the differential diagnosis.

A measles outbreak in 2019 infected over 1200 people in 31 states (CDC, 2019b). Prior to the appearance of the classic morbilliform rash, there is a febrile prodrome usually lasting 2–4 days with fever, malaise, anorexia with subsequent development of conjunctivitis, coryza and cough (Moss, 2017). Measles should be considered in children with high fever and cough who are unimmunized or immunosuppressed and live in or have recently traveled to an area experiencing a measles outbreak. Pneumonia is a known complication of measles and the most common cause of death in children with recent measles infection.

Diagnosis

Imaging

Chest radiography has long been considered the reference standard for the diagnosis of pneumonia in high resource settings. Despite the reliance on chest radiography, it is neither 100% sensitive nor 100% specific; however, one study found that a negative chest radiograph has a negative predictive value of 98.8%, therefore a negative chest radiograph excludes pneumonia in the majority of children (Upset et al., 2018). Additionally, it cannot routinely differentiate between viral and bacterial etiologies of pneumonia (Swingler, 2000) (Fig. 2 and B). The interobserver agreement in one systematic review demonstrated a kappa of 0.26–0.70, ranging from fair to excellent in identifying bacterial pneumonia (Swingler, 2000). Generally, the presence of alveolar infiltrates on chest radiograph is a reliable indicator of radiographic pneumonia, but other findings, such as interstitial infiltrates, hilar adenopathy and air bronchograms are less reliable (Neuman et al., 2012). It may also be difficult to differentiate atelectasis versus consolidation (Novack et al., 2006), which can lead to an overdiagnosis of pneumonia and increased antibiotic use. For this reason, in addition to the risk of ionizing radiation, it is important to use chest radiography only where the information gained has the potential to change clinical management rather than reflexively in all patients.

Although many findings on chest radiograph are not specific for bacterial pneumonia, certain findings may be suggestive of particular etiologies. Significant hilar adenopathy may suggest fungi, M. pneumoniae or M. tuberculosis. Nodular infiltrates may be seen with Pneumocystis jiroveci, fungi, viruses and atypical bacteria. Pneumatoceles are frequently detected in children with pneumonia secondary to S. aureus.

Given the challenges of chest radiography, significant variation exists in its use to diagnose pneumonia. (Neuman et al., 2011) The necessity of chest radiographs depends on the setting and severity of illness. The 2011 Infectious Diseases Society of America (IDSA) and Pediatric Infectious Diseases Society (PIDS) guideline on pediatric CAP recommends against routine chest imaging in children who are well enough to be treated as outpatients after clinical evaluation. Children with hypoxemia (oxygen saturation ≤ 90%) or significant respiratory distress should have chest radiographs performed. There is some data to suggest that a two-view (posteroanterior and lateral) radiograph is more accurate than one-view; a two-view is recommended by the PIDS/IDSA guideline, while the British Thoracic Society guideline recommends against lateral radiographs. A lateral radiograph should

![Fig. 2](A and B) PA and lateral chest radiograph demonstrating a right middle lobe consolidation consistent with pneumonia. Image Courtesy of Russ Horowitz, MD.)
never be performed on its own. Additionally, radiographs should be obtained in patients who have failed outpatient antibiotic therapy or are hospitalized. Radiographs in these situations can help identify pattern of infiltrate and any complications of pneumonia, such as empyema or parapneumonic effusions (Bradley et al., 2011). Chest computed tomography should be considered in situations where potentially severe findings on chest radiography, such as nodular infiltrates, abscesses, necrotizing pneumonia or moderate-to-large effusions, need to be further delineated.

Lung ultrasound is being increasingly used in the diagnosis of pneumonia (Boursiani et al., 2017). Benefits include portability and lack of radiation. There are currently no formal guidelines on the indication for ultrasound use. Historically, ultrasound has been most frequently used for evaluating complications of pneumonia (i.e., parapneumonic effusion or empyema), but studies have demonstrated high sensitivity, specificity and interrater reliability for detecting lung consolidation when compared to chest radiography (Pereda et al., 2015) (Fig. 3 and B). A meta-analysis found a pooled sensitivity for the diagnosis of pneumonia with a linear probe to be 96% and specificity of 93% with a positive likelihood ratio of 15.3 and negative likelihood ratio of 0.06 (Pereda et al., 2015). A challenge in interpreting these studies is the use of chest radiography, an imperfect standard, as the gold standard for which to compare lung ultrasound. In a recent randomized trial in which patients underwent chest radiography followed by ultrasound versus ultrasound and chest radiography only if there was diagnostic uncertainty for pneumonia, there was a significant reduction in chest radiography use in the ultrasound first group that varied based on the operator’s ultrasound experience. In this study, there were no missed cases of pneumonia (Jones et al., 2016). Given the operator-dependent nature of lung ultrasound, it will be important for emergency providers to be trained to be competent with this imaging modality (Balk et al., 2018; Tsou et al., 2019; Gravel et al., 2020).

Follow-Up Imaging
Routine follow-up chest radiographs are not recommended in children who improve with outpatient or inpatient management of CAP (Bradley et al., 2011). Repeat chest radiographs are recommended in children who do not improve or deteriorate within 48–72 h of antibiotic therapy or in patients with complicated pneumonia with worsening respiratory distress (Bradley et al., 2011). Patients with recurrent pneumonia involving the same lobe or those with lobar collapse at diagnosis should have repeated films in 4–6 weeks to evaluate for possible underlying predisposition to lobar collapse such as anatomic anomaly, chest mass or foreign body aspiration (Bradley et al., 2011).

Laboratory Testing
Blood cultures
Blood cultures are not routinely recommended in otherwise healthy, immunized children with mild CAP and planned outpatient treatment due to their very low yield (<2%, less than the typically reported blood culture contamination rate) (Bradley et al., 2011). The 2011 IDSA/PIDS pediatric CAP guideline recommends obtaining blood cultures in children with moderate to severe disease who require hospitalization for CAP, but these cultures tend to be low-yield with a rate of bacteremia of 2.5–7% (Bradley et al., 2011; Myers et al., 2013; Neuman et al., 2017). In one large retrospective study of over 7500 patients admitted to U.S. hospitals with CAP, 0.15% of the cohort and 0.43% of those with blood cultures obtained grew an organism not susceptible to penicillin (Neuman et al., 2017). Given the low rate of bacterial growth, it is reasonable to apply a targeted approach to obtaining blood cultures in uncomplicated pneumonia. Patients who are incompletely immunized, have failed outpatient therapy, are less than
6 months old, have an indwelling central line or those with complicated pneumonia should have a blood culture obtained upon admission (Heine et al., 2013). Patients with complicated pneumonia, including those requiring pleural drainage, have higher rates of bacteremia (> 10%); thus, blood cultures should be routinely obtained in these patients (Shah et al., 2011; Myers et al., 2013). Ideally, blood cultures should be obtained prior to antibiotic administration. Rapid multiplexed assays on positive blood cultures now allow for earlier organism identification, curtailing the need to wait for final culture results to target antibiotic therapy (Sullivan et al., 2013).

Other Microbiologic Investigations

There are many challenges in the identification of a specific pathogen in pediatric CAP, including the very low yield of blood cultures, the potential for bacterial-viral co-infection and inability to directly sample from the lung. Table 3 summarizes the PIDS/IDSA guideline for specific pathogen testing.

Sputum culture is often used in adults with CAP, however young children cannot reliably produce sputum for culture. Expectorated sputum should be processed by the laboratory as soon as possible after sampling (ideally within 2 h) to avoid destruction of potential organisms or commensal organism overgrowth. An adequate sputum specimen is one with very few squamous epithelial cells (<10 per high-powered field) and sufficient volume white blood cells (>25 per high-powered field). In general, sputum gram stain and culture can be considered in older children (>8 years of age) who are hospitalized and can adequately produce sputum.

Of note, despite excellent sensitivity of the pneumococcal urine antigen test in adults, its sensitivity is lower due to the fact that children have an increased frequency of bacterial colonization with *S. pneumoniae* compared to adults, which leads to false positive results (Neuman and Harper, 2003; Florin and Ambroggio, 2014). Pneumococcal antigen testing of pleural fluid may be useful in identifying pneumococcal etiology of empyema (Le Monnier et al., 2006; Ploton et al., 2006; Martínón-Torres et al., 2012).

The diagnosis of *M. pneumoniae* can be challenging, as data on the natural course of disease or influence of antibiotic therapy is unclear. Testing for *M. pneumoniae* may be most useful in school-age children and adolescents with intermediate to high suspicion for atypical pneumonia to target macrolide therapy to those with highest likelihood of Mycoplasma infection. Traditional culture and cold-agglutinin methods for detection of Mycoplasma are challenging to perform or interpret and therefore are generally not recommended. Two current diagnostic options include serologies and PCR testing. Rapid serologic testing for IgM now exists, with sensitivities ranging from 74% to 96% and specificities ranging from 85% to 98% (Alexander et al., 1996; Dunn et al., 2004). Molecular testing via PCR is commercially available through multiplex syndromic respiratory panels. Specificity is generally high, but sensitivities vary (Zhang et al., 2011). Typically, these panels are available for viral and atypical pathogens. Lower respiratory tract panels that also include typical bacteria (e.g., *S. pneumoniae*) exist but at the current time are only indicated for lower respiratory samples, such as bronchoalveolar lavage specimens. Regardless of the panel, results of multiplex PCR panels need to be carefully interpreted in the context of the clinical picture to guide treatment decisions. *M. pneumoniae* has been detected in both symptomatic and asymptomatic children in similar proportions, with approximately 20% of children with the organism detected up to 2 months after initial detection (Spuesens et al., 2013). Given the varied sensitivities, it is important to be aware of local laboratory test performance to ensure proper interpretation.

Acute phase reactants

Complete blood counts are not routinely recommended in the evaluation of pneumonia in either the outpatient or inpatient settings, as white blood cell count is rarely useful to differentiate bacterial from viral infection or to prognosticate children with CAP (Nohynek et al., 1995; Korppi et al., 1997). Although white blood cell count (WBC) can be elevated in children with bacterial pneumonia, most children with CAP and an elevation of the WBC do not have a bacterial etiology. The degree of elevation also does not differentiate between bacterial and viral etiologies (Nohynek et al., 1995; Korppi et al., 1997; Purcell and Fergie, 2007). Similarly, C-reactive protein (CRP), an acute phase reactant produced by the liver in response to inflammatory cytokines, has low

### Table 3

| Pathogen testing | PIDS/IDSA guideline recommendations |
|------------------|-------------------------------------|
| Blood culture    | Failure of antibiotic therapy, progression of disease despite antibiotic therapy, moderate to severe disease requiring hospitalization |
| Sputum culture   | Hospitalized patients who can adequately produce sputum |
| Pleural fluid gram stain and culture | If pleural fluid specimen obtained |
| *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* testing | Obtain *Mycoplasma* testing in those with suspected atypical pneumonia (be aware of local test characteristics to aid interpretation); *Chlamydia pneumoniae* testing NOT recommended |
| Influenza testing | Sensitive and specific tests recommended during times of peak influenza activity |
| Other viral testing | Consider if result is likely to change clinical decision-making |
| Pneumococcal antigen | Not recommended in urine; consider in pleural fluid, if present |
| Polymerase chain reaction (PCR) | Pleural fluid PCR test for *Streptococcus pneumoniae* and *Staphylococcus aureus* |

From Florin TA and Ambroggio L (2014) Biomarkers For Community-Acquired Pneumonia In The Emergency Department. *Current Infectious Disease Reports*. doi: 10.1007/s11908-014-0451-8.
sensitivity to differentiate bacterial from viral or atypical pneumonia (Nohynek et al., 1995; Korppi et al., 1997). CRP levels >3.5 mg/dl have been shown to weakly predict bacterial CAP in one meta-analysis (Flood et al., 2008), though there was a large range of reported sensitivities and specificities. Given its relatively weak predictive performance, current guidelines do not recommend the routine measurement of acute-phase reactants in children with pneumonia and do not support the use of these biomarkers to differentiate between viral and bacterial pneumonia (Bradley et al., 2011).

Procalcitonin (PCT), a precursor of calcitonin that is secreted by multiple tissues in response to bacterial infection, is generally not present in healthy individuals, but rises 4–6 h after an infectious insult. Conflicting data exist on the ability of PCT to discriminate bacterial from viral infection, with PCT concentrations often overlapping in bacterial and viral disease. In general, PCT concentrations are higher in children with bacterial infection compared with viral or atypical pathogens; however, its greatest potential appears to be identifying a group of patients at lower risk for invasive bacterial infection, informing a decision to not treat with antibiotics. One study found that a PCT < 0.1 ng/mL had a negative predictive value of 1.00, with no patient with a PCT < 0.1 ng/mL having a typical bacterial source detected by comprehensive methods (Stockmann et al., 2018). Another study found that a PCT of ≤0.5 ng/mL ruled out pneumococcal pneumonia in >90% of cases and that a PCT ≥1.5 ng/mL CAP with a positive pneumococcal urinary antigen had a positive likelihood ratio of 4.6 (Galetto-Lacour et al., 2013). A meta-analysis of more than 6000 adults with CAP in more than 25 studies found that when an algorithm guiding the use of antibiotics (antibiotics recommended when PCT > 0.25 ng/mL and not recommended when PCT < 0.25 ng/mL) was compared with standard care, those using PCT guidance had less antibiotic exposure with fewer antibiotic-associated adverse effects, but no differences in mortality, treatment failure, or length of stay (Schuetz et al., 2018). Data in children is more limited, and more studies are needed to further delineate the role of PCT in the diagnosis and exclusion of bacterial pneumonia.

**Indications for Hospitalization**

Wide variation in the rates of hospitalization for CAP exist at different U.S. children’s hospitals emergency departments (EDs), with hospitalization rates ranging from 10% to 68% in one study (Florin et al., 2013). In this study, EDs that used the more diagnostic testing admitted a higher proportion of patients; however, there was no difference in the rate of hospital revisits between the hospitals, suggesting that some of these admissions may be avoidable (Florin et al., 2013). The decision for hospitalizing a child with pneumonia is dependent on many factors including the age of the child, the predicted clinical course, presence or absence of respiratory distress and hydration status. Unfortunately, there are no validated severity scales to aid clinicians with this decision as there are in adults (Fine et al., 1997; Lim et al., 2003). General recommendations for disposition are summarized in Table 4 and include the following: age less than 3 months, hypoxia <90%, tachypnea based on age, respiratory distress (retractions, nasal flaring, grunting, dyspnea), apnea, dehydration, concern for a virulent organism such as MRSA, or if family is unable to observe the child at home for clinical deterioration (Bradley et al., 2011; Seiden and Callahan, 2016; Dean and Florin, 2018).

**Table 4  Recommendations for disposition of children with community-acquired pneumonia.**

| Age | Mild Consider Outpatient Treatment | Moderate Consider Inpatient Treatment | Severe Consider Intensive Care |
|-----|-----------------------------------|--------------------------------------|--------------------------------|
| General Appearance | ≥3 months Nontoxic | <3 months Ill appearing | Severe mental status changes Apnea, severe respiratory distress, inadequate ventilation |
| Work of Breathing | Absence of chest indrawing, grunting, nasal flaring or apnea | Moderate dyspnea (chest indrawing, grunting, nasal flaring) | |
| Pulse Oximetry | >90% in room air | <90% in room air | <90–92% despite 40% FiO2 via high-flow nasal cannula or 50% FiO2 via face mask; or inability to transition from 100% nonrebreather mask |
| Respiratory Support | None | Consider if high-flow nasal cannula with limited oxygen need | New or increased positive-pressure ventilation (CPAP, BiPAP, mechanical ventilation/artificial airway); impending respiratory failure |
| Hydration | Ability to tolerate oral fluids and medications | Dehydration or inability to tolerate oral fluids and medications | Systemic signs of inadequate perfusion (hemodynamic instability, mental status changes, severely cool extremities) |
| Complicated Pneumonia | Not present | Moderate to Large parapneumonic effusion | Parapneumonic effusion requiring chest drainage |
| Adequate Follow-Up | Ability to ensure adequate outpatient follow-up | Cannot ensure outpatient follow-up or failure of initial outpatient management | |

Seiden J and Callahan J (2016) Chapter 90. In: Fleisher & Ludwig’s Textbook of Pediatric Emergency Medicine, 7th edn., pp. 600–604. Wolters Kluwer.
**Treatment**

**Outpatient Therapy**

The causative agent of CAP is usually not identified, particularly in the outpatient setting, therefore antibiotic treatment is generally targeted towards the most common bacterial organisms. In 2011, the Infectious Diseases Society of America (IDSA) and Pediatric Infectious Diseases Society (PIDS) published joint guidelines recommending antibiotic treatment by age group (Bradley et al., 2011). Table 5 summarizes the recommendations for empiric therapy of children with CAP. For immunized infants and children of all ages, high-dose amoxicillin (90 mg/kg/day divided twice daily) is recommended for children with mild-to-moderate CAP with presumed bacterial origin. (Bradley et al., 2011) This regimen adequately covers *Streptococcus pneumoniae*, the most common bacterial cause of bacterial CAP in this age group. For children with amoxicillin allergy, alternative antibiotic regimens include second- or third-generation cephalosporins, oral levofloxacin, or oral linezolid. (Bradley et al., 2011) The duration of therapy is typically 7–10 days (Bradley et al., 2011), however shorter courses of antibiotics have also been shown to be effective (Greenberg et al., 2014). For school-aged children and adolescents, a macrolide, most commonly a 5-day course of azithromycin, may be added if there is suspicion for atypical pathogens as *Mycoplasma pneumoniae* is more common in these age groups (Bradley et al., 2011). Macrolide monotherapy does not provide sufficient coverage for *S. pneumoniae*, and therefore should not be routinely prescribed (Ambroggio et al., 2016). During influenza season, targeted antiviral therapy against influenza should be started in high-risk patients in the setting of local influenza outbreaks or if the presentation is consistent with influenza (Bradley et al., 2011; Maldonado et al., 2019). High risk patients include children younger than 5, especially younger than 2 years of age, those with chronic pulmonary disease (e.g., asthma, cystic fibrosis, bronchopulmonary dysplasia) or compromised respiratory function, hemodynamically significant heart disease, renal disorders, hematologic disease including sickle cell and other hemoglobinopathies, metabolic disorders, immunodeficiency, neurologic or neurodevelopmental conditions, children on long-term aspirin therapy and those with extreme obesity.

**Inpatient Therapy**

Patients who are hospitalized for CAP generally require parenteral treatment. Narrow-spectrum therapy is preferred over broad, when appropriate (Table 5). In children under 1 month of age, ampicillin and an aminoglycoside or ampicillin and cefotaxime are recommended. In children 1–3 months of age, ampicillin or cefotaxime monotherapy may be appropriate. A macrolide should be added when *Bordetella pertussis* or *Chlamydia trachomatis* is suspected. Ampicillin is the first-line antibiotic in all immunized children over the age of 3 months with uncomplicated pneumonia (Bradley et al., 2011). Several studies have demonstrated no difference in clinical outcomes between children treated with narrow-spectrum (i.e., ampicillin) compared with broad-spectrum antibiotics (Newman et al., 2012; Williams et al., 2013; Queen et al., 2014; Thomson et al., 2015). For children with critical illness (i.e., those admitted to an intensive care unit), those who are unimmunized or incompletely immunized, or in areas with high pneumococcal resistance to penicillins, a third-generation cephalosporin (e.g., ceftriaxone) is recommended (Bradley et al.,

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**Table 5** Antibiotic therapy for empiric treatment of pediatric community-acquired pneumonia.

| Age                      | Bacterial pneumonia               | Atypical pneumonia               |
|--------------------------|-----------------------------------|----------------------------------|
| **Outpatient treatment** |                                    |                                  |
| 3 months to < 5 years    | Preferred: amoxicillin            | Preferred: azithromycin         |
|                          | Alternative: amoxicillin/clavulanate | Alternative: clarithromycin, erythromycin |
|                          | Preferred: amoxicillin            | Preferred: azithromycin         |
| 5–17 years               | Alternative: amoxicillin/clavulanate | Alternative: clarithromycin or erythromycin. |
|                          | Alternative: amoxicillin          | Preferred: azithromycin         |
|                          | Alternative: amoxicillin/clavulanate | Alternative: clarithromycin or erythromycin. Doxycycline if > 7 years old. |
| **Inpatient treatment**  |                                    |                                  |
| 3 months to 17 years, immunized against *Haemophilus influenzae* type B and *Streptococcus pneumoniae*; minimal local pneumococcal resistance to penicillins | Preferred: ampicillin or penicillin G | Preferred: Azithromycin with a β-lactam |
|                          | Alternatives: ceftriaxone or cefotaxime; add clindamycin or vancomycin for suspected MRSA | Alternatives: clarithromycin or erythromycin. Doxycycline for children > 7 years old. |
| 3 months to 17 years, not fully immunized against *Haemophilus influenzae* type B and *Streptococcus pneumoniae*; significant local pneumococcal resistance to penicillins | Preferred: ceftriaxone or cefotaxime | Preferred: Azithromycin with a β-lactam |
|                          | Alternative: levofloxacin         | Alternatives: clarithromycin or erythromycin. Doxycycline for children > 7 years old. |
|                          | Add vancomycin or clindamycin for suspected MRSA |                                  |

Adapted from Bradley JS, et al. (2011). The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the pediatric infectious diseases society and the infectious diseases society of America *Clinical Infectious Diseases*, 53(7): 1–52. doi: 10.1093/cid/cir531. Table 7: Empirc Therapy for Pediatric Community-Acquired Pneumonia (CAP).
If there is a suspicion for an atypical pathogen or if patients are not improving with the aforementioned antibiotic regimens, a macrolide can be added to the beta-lactam therapy (Bradley et al., 2011). In critically ill children with sepsis or empyema, vancomycin should also be added (Bradley et al., 2011). Antiviral therapy should be started in patients with moderate to severe CAP in the setting of local influenza outbreaks or if the presentation is consistent with influenza (Bradley et al., 2011).

**Disease Complications**

The majority of viral pneumonias resolve with supportive care. In infants, particularly those with a history of prematurity, there is a risk of apnea with respiratory syncytial virus. *Chlamydia* or *B. pertussis* (Ralston and Hill, 2009). Some patients may require hospitalization for dehydration in the setting of congestion or increased work of breathing.

Bacterial pneumonia is expected to respond to antibiotic treatment within 48–72 h. Patients returning to care with worsening symptoms after this timeframe or those hospitalized with failure to improve or clinical deterioration should be evaluated for complications of pneumonia (i.e., empyema, pleural effusion, pneumatocele), a resistant organism, viral etiology, or coinfection and merit repeat radiographs (Bradley et al., 2011). *S. aureus*, in particular, is associated with pulmonary abscess, empyema and pneumatocele. *Mycoplasma* pneumonias have a distinct set of complications including pleural effusions and extrapulmonary complications including arthritis, meningitis, and *Mycoplasma*-induced rash and mucositis (MIRM) which is most often seen in males with a mean age of 12 years old (Canavan et al., 2015). Pneumonia can also cause systemic complications including sepsis, disseminated intravascular coagulopathy and hemolytic-uremic syndrome.

**Prevention**

The introduction of the protein conjugate vaccines against *H. influenzae* and *S. pneumoniae* have resulted in declines in the prevalence of bacterial pneumonia (Morris et al., 2008; Pilishvili et al., 2010; Halasa et al., 2013; Kaplan et al., 2015). These vaccines are part of routine immunization schedules in many countries; increased access to these vaccines is critical to low-middle income countries where the morbidity and mortality due to CAP is greatest. Influenza vaccine should be provided annually to all children 6 months and older. This vaccine has been shown to decrease mortality and complications of influenza, in addition to potential risk for secondary bacterial pneumonia in conjunction with influenza (Allison et al., 2006; Maldonado et al., 2019). In addition to immunizing children, national guidelines recommend immunization parents and close contacts against influenza and other vaccine-preventable diseases.

**Summary**

Pediatric pneumonia is an important contributor to morbidity and mortality globally and remains a costly condition in the United States accounting for the highest number of days of antibiotic use in U.S. children’s hospitals (Gerber et al., 2013). The clinical diagnosis is challenging due to overlapping phenotypes of viral and bacterial etiologies of pneumonia and many other lower respiratory tract pathologies such as asthma and bronchiolitis. Auscultatory findings are less reliable than hypoxemia and increased work of breathing in the clinical diagnosis of pneumonia. Chest radiography remains the reference standard for diagnosing pneumonia, but other modalities such as ultrasound are gaining traction. In all pediatric age groups excluding neonates, viral pathogens are the most common etiology of pneumonia, with *S. pneumoniae* as the most common typical bacterial pathogen. *M. pneumoniae* detection increases with increasing age, particularly in children 5 years and older. Diagnostic testing should be focused to those at intermediate to high risk for pathogen detection (e.g., complicated pneumonia, immunocompromised) or in those where diagnostic testing results will change management (e.g., intermediate to high risk of *M. pneumoniae*). Treatment for presumed bacterial pneumonia should begin with narrow-spectrum beta-lactams but broadening to third-generation cephalosporins may be appropriate in certain situations such as failed outpatient therapy or critical illness requiring intensive care unit admission.

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