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# Community-Acquired Pneumonia In Children

*Penelope H. Dennehy, MD*

**Community-acquired pneumonia (CAP)** is one of the most common infections encountered in pediatrics, with an annual incidence of approximately 40 cases per 1000 children in North America.<sup>1</sup> Despite its frequency, CAP in children remains difficult to diagnose, evaluate, and manage because many pathogens may be responsible, co-infections occur frequently, clinical features may vary widely, and laboratory testing to support the diagnosis is limited.

## ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA

Many pathogens cause pneumonia in children, including bacteria, viruses, and fungi. Because culture of lung parenchyma or pleural fluid requires an invasive procedure, most studies in children have relied on indirect methods such as rapid viral testing or **polymerase chain reaction assay (PCR)** on upper respiratory tract secretions, serology, and/or blood culture to identify the infecting pathogen. Studies that include an intensive search for etiology in hospitalized children with pneumonia identified a likely cause in up to 85% of cases, but an etiologic diagnosis is made in a much smaller proportion of outpatient cases. Due to a reluctance to perform invasive diagnostic procedures on young children, the epidemiology of CAP in children remains poorly defined.

The most common etiologies of pneumonia vary with the age of the patient (Table 1). In neonates, group B streptococcus and gram-negative enteric bacteria are the most common bacterial pathogens and are generally acquired through vertical transmission.<sup>2</sup> Viral pneumonia with cytomegalovirus and herpes simplex virus should be considered even without a suspicious maternal history. *Chlamydia trachomatis* infection, once a common cause of infection in infants, has become much less common through prenatal screening and treatment of maternal infection.

The most common cause of bacterial pneumonia in children older than 3 weeks is *Streptococcus pneumoniae*. Before the pneumococcal vaccine was introduced in 2000, *Streptococcus pneumoniae* accounted for 13% to 28% of pediatric CAP.<sup>3</sup> Post-licensure epidemiologic studies show that all-cause pneumonia hospitalizations in children under age 2 in the United States have decreased by 39%, providing further evidence of the role of pneumococcus as a major cause of childhood CAP.<sup>1, 4, 5</sup>

Group A streptococcus, *Staphylococcus aureus*, *Haemophilus influenzae* type b, and *Moraxella catarrhalis* are less common bacterial causes of pneumonia. The organisms *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (formally *Chlamydia pneumoniae*) commonly cause CAP in school-age children and adoles-

cents, although they may infect preschool-age children more commonly than generally recognized. In one study, the age of patients with atypical infection ranged from 9 months to 13 years, with 47% of infections occurring in those aged younger than 5 years.<sup>6</sup> *Bordetella pertussis* should be considered in young or unimmunized children with paroxysmal cough, whoop, posttussive emesis, or apnea. Tuberculosis should also be considered if the patient has suggestive clinical signs, has recently been to an endemic area, or has had contact with an individual with active tuberculosis.

Most cases of CAP in preschool-age children are caused by viruses, including **respiratory syncytial virus (RSV)**, adenovirus, parainfluenza 1, 2 and 3, influenza A and B, human metapneumovirus, and rhinoviruses. Preceding viral illness is thought to play a part in the pathogenesis of bacterial pneumonia. A study by Ampofo and colleagues recently showed a strong temporal association between confirmed viral respiratory illness with RSV, influenza, and human metapneumovirus and invasive pneumococcal disease over six winter seasons.<sup>7</sup> Although their data do not prove causation, rates of invasive pneumococcal disease rose in close association with the diagnosis of respiratory viral illnesses each winter season.

Mixed infections may occur in 30% to 50% of children with CAP, including

*Streptococcus pneumoniae* and a virus, *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*, and *Streptococcus pneumoniae* and *C. pneumoniae*.<sup>3, 6</sup>

### EVALUATION AND DIAGNOSIS

Children with fever, tachypnea, increased work of breathing, and an abnormal respiratory examination require evaluation for pneumonia. Goals of this evaluation include diagnosis and determination of likely etiologies while recognizing limitations of current diagnostic methods.

### Clinical Assessment

Children with CAP present with various clinical signs and symptoms. Symptoms and signs of pneumonia include fever, cough, tachypnea, nasal flaring, grunting, retractions, poor feeding, irritability, rales, and hypoxia, and the presence of these findings varies depending on the patient's age and the severity of illness. There is often a history of a preceding viral upper respiratory tract infection.

Although most present with fever and respiratory symptoms, such as cough and tachypnea, some children with pneumonia present with less classic symptoms, such as abdominal pain, nausea, vomiting, or chest pain. Abdominal pain may occur in patients with basilar pneumonia and at times is the most prominent complaint and may be mistaken for appendicitis. In a study of children admitted for abdominal pain, pneumonia was ultimately found to be causative in 1.6% of patients.<sup>8</sup>

Wheezing and exacerbation of underlying asthma are symptoms more typically encountered in patients with pneumonia caused by viruses and atypical bacteria such as *Mycoplasma pneumoniae* and *C. pneumoniae*. Symptoms such as headache, low-grade fever, pharyngitis, and cough usually precede signs of lower respiratory tract infection by 5 to 7 days in patients with atypical bacterial pathogens.

Multiple studies have sought to identify clinical variables that can be used to make an accurate clinical diagnosis of

**Table 1. Common Pathogens in Community-Acquired Pneumonia By Age**

Age	Etiology	
	Bacterial	Viral
Birth to ≤ 3 months	Group B streptococci Gram-negative enteric bacilli <i>Streptococcus pneumoniae</i> <i>Bordetella pertussis</i> <i>Chlamydia trachomatis</i> <i>Staphylococcus aureus</i> <i>Listeria monocytogenes</i>	Respiratory syncytial virus Influenza A&B Parainfluenza viruses 1, 2 & 3 Human metapneumovirus Rhinovirus Adenovirus
3 months to 5 years	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydophila pneumoniae</i> <i>Haemophilus influenzae</i> Moraxella catarrhalis <i>Staphylococcus aureus</i> <i>Streptococcus pyogenes</i>	Respiratory syncytial virus Influenza A&B Parainfluenza viruses 1, 2 & 3 Human metapneumovirus Rhinovirus Adenovirus
5 years and older	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydophila pneumoniae</i> <i>Staphylococcus aureus</i>	Influenza A&B

pneumonia. These studies found that no single clinical variable offers significant accuracy, although tachypnea has the highest sensitivity (45%-80%) and specificity (54%-75%).<sup>9-11</sup> Combining tachypnea, rales, and increased respiratory effort raises the specificity for a clinical diagnosis of pneumonia to 84%, but lowers the sensitivity to only 43%, thus missing a significant portion of patients with pneumonia, since the majority of patients do not have all three findings on examination.<sup>11</sup> A 1997 Canadian study concluded that the absence of tachypnea, crackles, decreased breath sounds, and respiratory distress effectively excludes pneumonia.<sup>9</sup> However, a subsequent study found that the sensitivity and specificity of these guidelines were only 45% and 66%, respectively.<sup>12</sup> The absence of crackles or rales does not preclude the diagnosis of pneumonia. Other signs of increased work of breathing, such as nasal flaring and retractions, increase the likelihood of pneumonia but are not highly sensitive or specific, as bronchiolitis may present similarly.

The World Health Organization (WHO) suggests that tachypnea and retractions are the most accurate signs for identifying pneumonia and should be used to guide management in areas with limited access to radiography. The WHO defines tachypnea as 50 breaths/min in infants 2 to 12 months of age, 40 breaths/min in children aged 1 to 5 years, and 20 breaths/min in children aged 5

years and older. Respiratory rate should be measured over 60 seconds due to variations in respiratory rate from periodic breathing and behavioral factors.

No single clinical sign reliably predicts hypoxia, although inability to breastfeed, grunting, or central cyanosis suggests it.<sup>13</sup> Oxygen saturation should be measured in patients with respiratory distress or ill appearance.

### Laboratory and Radiologic Assessment

In outpatients the diagnosis of CAP does not generally require laboratory studies or radiographs. Patients requiring hospitalization typically undergo diagnostic evaluation, although a standard laboratory work-up has not been defined.

Most studies do not demonstrate a higher likelihood of bacterial infection in patients with high temperature or elevated white blood cell count.<sup>3, 14</sup> Acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate have low specificity for bacterial pneumonia.<sup>3</sup>

Blood cultures may provide useful microbiologic data, including antibiotic sensitivities, and are often obtained in hospitalized children with suspected pneumonia. However, with the use of the Hib and pneumococcal conjugate vaccines, the risk of bacteremia is extremely low in outpatients older than 2 months of age with uncomplicated CAP.<sup>15, 16</sup> The rate of positive blood cultures may be higher in hos-

**Table 2. Antimicrobial Therapy in Community-Acquired Pneumonia Based on Age**

Age	Therapy Outpatient	Inpatient	Inpatient Complicated Pneumonia
Birth to 30 days	Not recommended	IV ampicillin + gentamicin	IV ampicillin + cefotaxime*
4 weeks to ≤ 3 months	Oral erythromycin# or azithromycin if <i>C. trachomatis</i> or <i>Bordetella pertussis</i> is suspected or confirmed	IV cefotaxime or ceftriaxone ± ampicillin§	IV cefotaxime or ceftriaxone ± ampicillin§*
3 months to 5 years	<b>Preferred:</b> high-dose oral amoxicillin ± azithromycin^ <b>2<sup>nd</sup> line:</b> oral clindamycin or oral third generation cephalosporin (cefdinir or cefpodoxime)	<b>Preferred:</b> IV ampicillin ± azithromycin^ <b>2<sup>nd</sup> line:</b> IV clindamycin or cefotaxime or ceftriaxone	<b>Preferred:</b> IV clindamycin + cefotaxime or ceftriaxone <b>2<sup>nd</sup> line:</b> IV vancomycin + cefotaxime or ceftriaxone
5 years and older	<b>Preferred:</b> azithromycin ± high-dose oral amoxicillin <sup>e</sup> <b>2<sup>nd</sup> line:</b> oral clindamycin or oral third generation cephalosporin (cefdinir or cefpodoxime)	<b>Preferred:</b> IV ampicillin ± azithromycin^ <b>2<sup>nd</sup> line:</b> IV clindamycin or cefotaxime or ceftriaxone	<b>Preferred:</b> IV clindamycin + IV cefotaxime or IV ceftriaxone <b>2<sup>nd</sup> line:</b> IV vancomycin + IV cefotaxime or IV ceftriaxone

\* IV vancomycin or clindamycin should be considered if there is concern for MRSA.

# Erythromycin is generally avoided in patients aged 6 weeks or younger because of an association with pyloric stenosis.

§ Add ampicillin if *Listeria* is suspected.

^ Consider adding azithromycin if symptoms persist despite ampicillin.

<sup>e</sup> Azithromycin monotherapy may be used if there is a high level of suspicion for atypical pathogens. If the patient does not improve after 48 hours of treatment, high-dose amoxicillin may be added.

pitalized patients or those with pneumonia complicated by empyema.

Testing outpatients with uncomplicated CAP to determine etiology generally is not indicated. Hospitalized patients with pneumonia are often tested for cohorting purposes or to facilitate selection of antibiotic therapy. Bacterial cultures of nasopharyngeal secretions have low accuracy because upper airway flora may differ significantly from lower airway pathogens.<sup>9</sup> Older patients may be able to produce a sputum sample for Gram stain and culture. Sputum cultures must be interpreted cautiously, however, due to potential contamination with colonizing oropharyngeal flora. A high-quality sputum specimen should have few squamous epithelial cells (≤10 per high-powered field) and numerous white blood cells (≥25 per high-powered field) on Gram stain. Patients with symptomatic pleural effusions should have pleural fluid obtained prior to antibiotic administration, when possible. Gram stain and bacterial culture of pleural fluid should always be performed in patients with pneumonia who have had pleural fluid drainage.

Rapid tests are often used for RSV and influenza, while cultures are often

available for parainfluenza, adenovirus, and other pathogens. Testing for human metapneumovirus and multiplex PCR assays for a panel of respiratory viruses are also available in some laboratories. Because multiple studies have demonstrated a high prevalence of co-infections or superinfections, isolation of a virus does not rule out the possibility of bacterial infection.<sup>6, 17, 18</sup>

*Chlamydia trachomatis* (in neonates) and *C. pneumoniae* can be detected via PCR although prolonged shedding can occur causing PCR tests remain positive outside a period of active disease. Both of these pathogens can otherwise be diagnosed by acute and convalescent serologies. For neonates and young infants direct fluorescent antibody testing can also be used on conjunctival and respiratory specimens for the diagnosis of *Chlamydia trachomatis*.

*Mycoplasma pneumoniae* is the most reliably detected by serologic testing in paired specimens obtained 2 to 3 weeks apart; a fourfold or greater rise in the antibody titers indicates a recent or current infection. Unfortunately, results of serologic testing rarely are available in time to influence clinical management. PCR testing is also available for the diagnosis of *M. pneumoniae* in some laboratories.

Although often considered the gold standard for diagnosis of pneumonia, chest radiography is not essential to diagnose pneumonia, particularly in outpatients. A 2005 Cochrane review found no evidence that chest radiographs improve outcome in ambulatory children with acute lower respiratory tract infections.<sup>19</sup> Chest radiography should be considered in highly febrile patients without another identifiable source especially those with tachypnea or a peripheral leukocytosis.<sup>20</sup> Confirmatory chest radiography is not necessary, however, in patients with classic findings of community-acquired pneumonia such as high fever, tachypnea and rales on physical examination. Imaging should be considered in patients when the diagnosis is unclear, in those not responding to antibiotic therapy, and in those with possible complications such as pleural effusion or empyema. In patients with complications of pneumonia, chest ultrasound or chest computed tomography may further guide management.

Certain chest radiography findings in patients with pneumonia can suggest a particular etiology although studies suggest that chest radiographs alone do not accurately differentiate between etiolo-

gies.<sup>3</sup> Bacterial pneumonia tends to be lobar although *Staphylococcus aureus* can cause a patchy bronchopneumonia. Viral and atypical bacterial pathogens, such as *Mycoplasma pneumoniae*, tend to cause interstitial infiltrates on chest radiography. However, atypical bacterial pathogens occasionally cause lobar infiltrates. Small parapneumonic effusions can also be seen with bacterial, viral, or atypical pneumonia. Severe bacterial pneumonias can cause loculated effusions or empyemas. Hilar lymphadenopathy and nodular disease suggest tuberculosis, or endemic mycoses such as *Histoplasma* or *Coccidioides*. Pneumatoceles are often seen in pneumonias caused by *S. aureus* and occasionally *Streptococcus pneumoniae*.

## MANAGEMENT

Management of children with CAP depends on the severity of disease and the patient age. All febrile neonates should be hospitalized and undergo a complete evaluation for serious bacterial infection, including blood, urine, and cerebrospinal fluid cultures. Antibiotic therapy with ampicillin and cefotaxime or gentamicin should be initiated to cover suspected pathogens, including group B streptococcus and *Escherichia coli* and *Listeria monocytogenes*. Afebrile, well-appearing infants with presumed *C. trachomatis* pneumonia can be managed as outpatients with macrolide therapy and close followup.<sup>9</sup> Children older than 3 months with CAP can be managed as outpatients if they are not hypoxic, in respiratory distress, or dehydrated.<sup>21</sup> Hospital admission should be considered for patients younger than three months of age, patients with underlying disease (sickle cell disease, immunocompromised host, etc.), those with oxygen saturation of less than 92% on room air, those with severe respiratory distress or grunting, or dehydration or inability to take oral fluids and antibiotics, or if follow-up can not be assured. Outpatients should be seen 24 to 48 hours after diagnosis to monitor response to therapy and assess for complications such as empyema.

Choosing which children to treat with antibiotics is difficult as there are few criteria to accurately differentiate between viral and bacterial pneumonia. Many researchers suggest close follow-up without antibiotic therapy for young children with mild disease, in whom a viral

etiology is more likely.<sup>21</sup> If antimicrobial therapy is used, the choice of antibiotic is based on the most likely pathogen(s) in the patient's age group. (Table 2)

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## Although often considered the gold standard for diagnosis of pneumonia, chest radiography is not essential to diagnose pneumonia, particularly in outpatients.

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In outpatients aged 3 months to 5 years, oral amoxicillin 80 to 90 mg/kg/day divided 2 or 3 times daily is effective against most *Streptococcus pneumoniae* and is considered first-line therapy.<sup>22</sup> High-dose amoxicillin is typically chosen to account for the possibility of resistant *Streptococcus pneumoniae*, whose resistance can be overcome at higher drug concentrations. In patients with penicillin allergy an appropriate alternative treatment is clindamycin which provides excellent pneumococcal coverage. Oral third-generation cephalosporins or macrolide can also be considered for patients with penicillin allergy. However it is important to note that these antibiotics are not as effective anti-pneumococcal agents as penicillins and macrolide resistance among pneumococcal strains is increasing.<sup>23</sup> A macrolide may be added to amoxicillin, as atypical infections may be more common in younger children than generally recognized.

For outpatient management of children over age 5 years, azithromycin is typically the drug of choice due to the prevalence of atypical pathogens. Azithromycin 10 mg/kg/day on day 1 followed by 4 additional days of 5 mg/kg/day is usually effective, although some experts suggest a 7- to 10-day course.<sup>24</sup> In the United States, approximately 15% of *Streptococcus pneumoniae* show resistance to macrolides; therefore, if the patient does not improve

after 48 hours of treatment, high-dose amoxicillin may be added.<sup>25</sup>

Antimicrobial choice for inpatients is usually empiric and depends on the patient's age and most likely pathogen. Ampicillin, ampicillin-sulbactam, and cephalosporins such as ceftriaxone may be used in hospitalized children.<sup>24</sup> Fluoroquinolones are rarely used in young children. Trimethoprim-sulfamethoxazole is suggested by the WHO as first-line therapy for treatment of CAP in cases that are not severe, although a Cochrane review has shown it to be less effective than amoxicillin.<sup>26</sup>

Methicillin-resistant *Staphylococcus aureus* (MRSA), while not a common cause of CAP, can cause a necrotizing pneumonia, especially in conjunction with influenza.<sup>27</sup> In cases where MRSA is suspected, clindamycin or vancomycin should be added. Clindamycin has been shown to be effective against MRSA, but local patterns of antibiotic susceptibility can vary.<sup>28</sup> Clindamycin should be considered for severe or necrotizing pneumonia in hospitalized patients if the frequency of clindamycin resistance among local MRSA isolates is less than 15%. If the frequency of clindamycin resistance is  $\geq 15\%$ , vancomycin should be used.

Levofloxacin is a fluoroquinolone effective against most resistant pneumococcal strains and atypical pathogens such as *Mycoplasma pneumoniae*.<sup>29</sup> These atypical pathogens should be considered in older patients as well as those with wheezing. Levofloxacin has broad coverage which makes it a useful therapy in patients with resistant isolates or significant drug allergies. While concerns of tendon rupture and other musculoskeletal injuries have prevented the approval of fluoroquinolones for children under age 18 data support safety in these patients.<sup>30</sup>

Patients with persistent symptoms or failure to improve after 48 hours should receive an initial or repeat chest radiography to detect a new or evolving pleural effusion. Some patients have small parapneumonic effusions that require no intervention, while others have significant bacterial infection in the pleural space that requires drainage. Current evidence favors surgical drainage within 48 hours of moderate large or large or loculated effusions, but prospective clinical trials are lacking.<sup>31</sup>

## PREVENTION

The leading causes of vaccine-preventable pneumonia in the United States are *Streptococcus pneumoniae* and influenza. Since routine childhood immunization with pneumococcal conjugate vaccine (PCV7) began in the United States in 2000, the overall incidence of invasive pneumococcal disease has decreased.<sup>5,26</sup> These declines have been tempered by concern about the emergence of other pathogens or other pneumococcal serotypes, including invasive serotypes such as 19A.<sup>32,33</sup> On February 24, 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed by the FDA for prevention of invasive pneumococcal disease caused by the 13 pneumococcal serotypes covered by the vaccine, including invasive serotypes such as 19A.<sup>34</sup>

In 2004-05, routine immunization for influenza was recommended for children aged 6 to 23 months. During seasons with a good match between vaccine and circulating influenza strains, efficacy approaches 70% to 90%.<sup>35</sup> In 2003-04, a year without good match, the protective effect for children 6 months to 8 years was only 23% and 51% against influenza-like illness and bacterial or viral (including influenza) pneumonia, respectively.<sup>36</sup> This study found that previously unvaccinated children under the age of 8 years require 2 doses for maximal protection against influenza. The current recommendations for influenza vaccine now recommend annual immunization for children aged 6 months to 18 years.<sup>37</sup> Children younger than age 9 years should receive two doses 4 weeks apart during their first immunization year.

## CONCLUSIONS

CAP represents a common and challenging pediatric problem. Diagnosis may be difficult because of limited laboratory testing, the broad range of pathogens, and the frequency of co-infections. Treatment typically targets the likely pathogen based on the patient's age. Future goals are to identify the most effective antimicrobial treatments for patients

with community-acquired pneumonia, to establish guidelines for treatment of children with CAP, to assess the impact of antimicrobial resistance, and to understand the long-term impact of immunization campaigns, especially against *Streptococcus pneumoniae* and influenza, on the development of CAP in children.

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