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Chapter 58

Pneumonia

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Key Points

- Causative pathogens of pneumonia in children can be difficult to identify.
- *Streptococcus pneumoniae* is the most common bacterial cause of pneumonia in children.
- Viral causes of pneumonia in children vary based on age and season.
- Tachypnea is the most reliable clinical predictor of pneumonia in children.
- Laboratory and radiologic testing offers limited diagnostic benefit.

Introduction and Background

Community-acquired pneumonia (CAP) is one of the most common infections in children and is the leading cause of mortality in children worldwide. Acute respiratory illnesses are responsible for more than 5 million fatalities each year in children less than 5 years of age in developing countries. The annual incidence in children less than age 5 is approximately 35 to 40 cases per 1000 in Europe and North America.[1] The mortality rate from pneumonia in children in the United States has declined by 97% from 1939 to 1996.[2] This decline is primarily attributable to the introduction of penicillin in the 1940s. Availability of the measles vaccine and improved access to medical care for poor children, primarily as a result of the Medicaid program, have contributed to further reduction in mortality rates recorded from 1963 to 1985. The rate of pneumonia remains high in developing countries. The World Health Organization (WHO) reported a global annual incidence of clinical pneumonia in children less than 5 years of age estimated to be 146.5 million new cases in developing countries and 2.1 million new cases in developed countries.[3] The definition of clinical pneumonia for the purpose of the WHO estimates encompasses pneumonia, bronchiolitis, and reactive airways disease associated with respiratory infections.

Recognition and Approach

Probably the greatest challenge in the approach to children with pneumonia is that the microbiologic etiology is difficult to identify. This is primarily due to limitations of diagnostic testing modalities: blood cultures, antigen testing and antibody titers, and the need for invasive means to retrieve specimens.[1,4] Two studies illustrate our limited ability to diagnose the etiology of pneumonia in children. In a prospective study of 168 *ambulatory* children with CAP, an etiologic agent was identified in only 43% of cases.[5] These included *Streptococcus pneumoniae* (27%), *Mycoplasma pneumoniae* (7%) and *Chlamydia pneumoniae* (6%). Patients with *S. pneumoniae* frequently had a mixed infection (40%). Of 157 patients tested for viral infection, 20% were positive by culture and/or direct fluorescent antibody test. Viral etiologies identified included respiratory syncytial virus (RSV), influenza viruses A and B, parainfluenza viruses 1 and 3, adenovirus, enterovirus, cytomegalovirus, and herpes simplex virus. All viral isolates were identified in children less than 8 years of age.[5] A similar study, in 254 *hospitalized* children with CAP, identified a potential causative agent in 85% of cases.[6] Extensive diagnostic testing accounted for the relatively high yield in this study. Similar etiologies identified, in decreasing frequency of occurrence, included *S. pneumoniae, Haemophilus influenzae, M. pneumoniae, Moraxella catarrhalis, C. pneumoniae, Streptococcus pyogenes,* and *Chlamydia trachomatis.* Viral etiologies included (most common to least common) RSV, rhinovirus, parainfluenza viruses 1 through 3, adenovirus, influenza virus A and B, coronavirus, human herpesvirus 6, Epstein-Barr virus, and varicella-zoster virus. Mixed viral-bacterial infections were detected in 30% of patients, and 41% of patients had more than one microbiologic agent identified. Of interest, of 93 patients with *S. pneumoniae,* only one had a positive blood culture. The remaining 92 patients were diagnosed based solely on serologic evidence.[6]

A prospective analysis seeking to identify etiologic agents via a pneumolysin-based polymerase chain reaction assay identified a respiratory pathogen in 79% of 154 pediatric patients with lower respiratory tract infection. The most common etiologic agent was *S. pneumoniae* (44%). Of 68 patients with *S. pneumoniae* infection, 18% had a co-infection with another bacteria and 31% had a co-infection with a virus. Atypical agents (*M. pneumoniae* and *C. pneumoniae*) accounted for 22% of all infections (14% and 9%, respectively). The most common viral etiologies included

influenza viruses A and B, RSV, parainfluenza viruses 1 through 3, and adenovirus.[7] While *S. pneumoniae* remains the most common bacterial cause for pneumonia in children, atypical infections are emerging as a common respiratory pathogen, particularly in adolescents.[8] In developing countries, aspiration from the upper respiratory tract accounts for nonserotypable *H. influenzae* as a cause of pneumonia in children.[9]

Published data reveal the limitations of diagnostic testing in pneumonia, with nearly 30% to 40% of cases unidentified. To aid management decisions, common patterns of infectious agents exist that help to guide diagnosis and therapy. Age is the most helpful marker for the cause of pediatric pneumonia. When considering age as a factor, *S. pneumoniae* remains the most common agent for all ages, and is reported as a causative agent in 15% to 35% of all childhood pneumonias. The atypical agents *M. pneumoniae* and *C. pneumoniae* are less common in children less than 5 years of age (<10%) and occur in increasing proportions in adolescents, reported as high as 50% in some studies. Viral etiologies, most commonly RSV, adenovirus, and influenza viruses A and B, are most common in infants and children less than 2 years of age (30%). The incidence of viral infection reduces dramatically with age.[1,4,10]

Other factors that aid in identifying the etiology of pneumonia include season and vaccine status. Viral infections, specifically RSV and influenza virus, peak in late fall and winter, though there is little seasonal influence on bacterial causes. Immunization status is also a helpful indicator of disease potential. Influenza infection is less likely if a child has received the influenza vaccine during the same season. *Haemophilus influenzae* type B vaccination eliminates the potential for this infection in children. The conjugated pneumococcal vaccine imparts partial protection from this pathogen as the causative agent.[4,10]

Clinical Presentation

Children with pneumonia present with a variety of clinical findings. Early findings are varied, and most cases present initially with symptoms of an upper respiratory infection. These may include low-grade fevers and rhinorrhea. Intermediate and late findings include fever, tachypnea, and cough. Several studies have sought to identify pneumonia based solely on clinical findings. These studies define the "gold standard" for pneumonia diagnosis as the chest radiograph.[11,12] Tachypnea was defined based on the WHO definition, as follows: in children less than 2 months old, respiratory rate (RR) greater than 60 breaths/min; in children 2 to 12 months old, RR greater than 50 breaths/min; and children older than 12 months, RR greater than 40 breaths/min.[13,14] In 1997, a Canadian task force developed an evidence-based guideline to diagnose pneumonia in children. This guideline states that, although no single clinical finding may accurately diagnose pneumonia, the absence of a cluster of signs, specifically respiratory distress, tachypnea, crackles, and decreased breath sounds, excludes the presence of pneumonia with a sensitivity of 100%.[1] These findings were applied to a cohort of 319 children who had a chest radiograph for possible pneumonia, 20% of whom had radiologic findings consistent with pneumonia. The Canadian guideline had a 45% sensitivity and 66% specificity for the diagnosis of pneumonia when applied to this patient cohort. Additionally, tachypnea was only 10% sensitive and 5% specific in this study.[15]

Despite these findings, several other studies have identified tachypnea as the best clinical indicator. A report on 572 children less than 2 years old, 7% with radiologic signs of pneumonia, defined tachypnea as having a 74% sensitivity and 76% specificity to identify pneumonia.[16] In a trial comparing clinical data to chest radiographs in 110 children, of 59 patients diagnosed with pneumonia, 35 had positive findings on chest radiograph. Of all clinical findings, the sensitivity to diagnose pneumonia was best for tachypnea (74%; specificity 67%), followed by retractions (71%) and rales (46%). Combinations of these improved specificity slightly, but did not improve sensitivity to recognize pneumonia. When the cohort was stratified by age, tachypnea was most sensitive: 83% in the youngest infants (<6 months old).[17] In a prospective study examining RR cutoffs for pediatric patients hospitalized with pneumonia, a RR greater than 57 in infants 2 to 11 months old, a RR greater than 48 in children 1 to 5 years old, and a RR greater than 36 in children more than 5 years old identified severe pneumonia requiring hospitalization.[18] These findings closely parallel the WHO definitions for tachypnea.

A prospective study of 570 children ages 1 to 16 years identified the following risk factors to be statistically significant in predicting pneumonia: history of fever, decreased breath sounds, crackles, retractions, grunting, fever, and tachypnea. A multivariate prediction model including fever, decreased breath sounds, crackles, and tachypnea had a sensitivity of 98%, but only an 8% specificity. Of note, fever and tachypnea alone were 93% sensitive for identifying pneumonia in this study.[19] This highlights the difficulty in predicting pneumonia based solely on clinical evaluation, though fever and tachypnea seem to strongly suggest the potential for lower respiratory infection and warrant further evaluation.

Pulse oximetry has also been examined as a predictor of pneumonia in children. Of 803 children less than 2 years of age who had a chest radiograph performed for respiratory symptoms, 80 (11%) had an opacity suggesting pneumonia. Mean pulse oximetry was not predictive of pneumonia in this cohort.[20] The addition of laboratory studies to aid diagnosis has been evaluated in several ways. A study of 154 hospitalized children with CAP, of whom 79% had an identifiable etiology, compared etiologies of pneumonia with respect to clinical and laboratory findings. This analysis revealed that wheezing was most commonly seen in patients with either a viral or an atypical bacterial etiology (41%) compared to patients who had a bacterial etiology (14%). Laboratory studies showed that bacterial etiologies were more likely to be associated with bandemia and elevated serum procalcitonin compared to viral or atypical causes. A multivariate logistic analysis of all variables identified two predictors of bacterial pneumonia: elevated temperature (>38.4° C) less than 72 hours after admission and presence of a pleural effusion, with a sensitivity of 79% and specificity of 59%.[7] Of 1248 febrile infants less than 60 days of age, three simple variables—rales, RR greater than 60 breaths/min, and absolute band count less than 1500/mm^3—identified 85% of infants with lobar pneumonia (85% sensitivity and 59% specificity).[21] It has been reported that, in a cohort of febrile children, leukocytosis as a sole diagnostic finding may indicate pneumonia, despite a lack of supportive clinical

findings. A prospective cohort study of 278 febrile (temperature > 39.0° C) children less than 5 years of age with a white blood count (WBC) greater than 20,000/mm^3 identified a lobar infiltrate in 26% of patients (36 of 146) who had a radiograph performed and no signs of pneumonia.[22]

Important Clinical Features and Considerations

Differentiating bacterial and viral causes of pediatric pneumonia remains a challenge to the emergency physician. Since treatment guidelines may be directly influenced by microbiologic causes, identifying bacterial pneumonia is an important goal. As already mentioned, the most helpful differentiating epidemiologic factor is age, since viral causes are more likely in children less than age 2 years; however, there is much overlap. The only clinical finding that correlates with viral infection is wheezing, yet specificity is low.[7] Laboratory evaluation has been used as an adjunct to help differentiate the cause of pneumonia. Serum procalcitonin, C-reactive protein (CRP), and interleukin-6 (IL-6) were measured in 126 children hospitalized for pneumonia. Children with bacterial pneumonia had higher serum procalcitonin and CRP concentrations than children with viral infections, though the specificity was low. If all three markers were elevated, the specificity for bacterial pneumonia was greater than 80%.[23] In a similar study, procalcitonin was found to be more sensitive and specific than CRP, IL-6, or WBC count for differentiating bacterial and viral causes of pneumonia in hospitalized children.[24] Despite these studies, procalcitonin has not become a widely used test in the evaluation of a child with pneumonia.

Radiographs have not been traditionally thought to be helpful in distinguishing viral from bacterial pneumonia, though alveolar infiltrates are suggestive of a bacterial etiology.[25-27] A systematic literature review of five studies examined this relationship and reported a low sensitivity and specificity of chest radiography in the identification of a bacterial etiology.[28] These studies are limited since there is no reliable reference standard. As mentioned previously, identifying the microbiologic etiology of childhood pneumonia is difficult, and therefore it is problematic to assess the diagnostic capability of a radiograph related to the microbiologic etiology; as a result, the test accuracy estimate of the radiograph may be falsely low.[28] A prospective report examined the influence of laboratory tests, specifically the WBC count, erythrocyte sedimentation rate, and serum CRP, in combination with the radiograph to aid in diagnostic capability.[29] In 254 children admitted to the hospital with pneumonia, a bacterial etiology was identified in 53%. Of these, 72% had an alveolar infiltrate (most commonly lobar) compared to 49% of patients with a viral infection. There was no difference between etiologies in patients with an interstitial infiltrate; 50% identified a bacterial etiology. Though there remains a fair amount of overlap, this study supports the finding that a lobar alveolar pattern is more likely to represent a bacterial etiology while an interstitial pattern does not differentiate between viral and bacterial infections. An elevated CRP (>80 mg/dl) suggested a bacterial cause (72% sensitivity and 52%specificity); however, laboratory findings did not significantly enhance the sensitivity of the radiograph in identifying a cause for pneumonia.[29]

Radiographic findings of focal consolidation suggest a bacterial etiology for pneumonia, although an atypical pneumonia (*Mycoplasma*) may also be represented, illustrating the lack of specificity to differentiate cause by radiograph findings alone. This overlap is exemplified when looking at a diffuse interstitial pattern. Given the proper clinical setting, atelectasis due to reactive airways disease may be indistinguishable from a viral or atypical process manifesting as a diffuse interstitial pattern. A unique finding that strongly supports a bacterial etiology is a "round pneumonia," which appears as a circular lesion in the retrocardiac area. A round pneumonia is most commonly caused by *S. pneumoniae* in children. Other possible infections include *H. influenzae, M. tuberculosis,* and *Klebsiella.* In the case of occult pneumonia in febrile children with leukocytosis,[22] round pneumonia is often discovered, despite few clinical respiratory findings.

In an effort to reduce radiation exposure and cost, the utility of the lateral chest radiograph was recently examined. In a review of 1268 children who had a chest radiograph, 19% with pneumonia, radiologists found the frontal view alone to have a sensitivity of 85% and specificity of 98% to diagnose pneumonia.[30] Pediatric emergency physicians found no difference in the sensitivity or specificity for identifying pneumonia on radiograph with or without the lateral view (91% vs. 87% sensitivity and 58% vs. 57% specificity, respectively).[31] The lateral view adds little diagnostic information for patients with lobar infiltrates; however, it may aid in diagnosing pneumonia in a small number of patients with a nonlobar infiltrate seen on the frontal view.

A systematic review identified a single trial examining the utility of the chest radiograph in diagnosing pneumonia in children. In 522 ambulatory children less than 5 years of age with a clinical diagnosis of pneumonia, there was no difference in outcome (time to recovery) when comparing children who had and did not have a chest radiograph performed.[32,33] Children who had a chest radiograph performed were more likely to receive antibiotic therapy and to be admitted to the hospital. When considering cost, inconvenience, and potential adverse effects associated with the chest radiograph, routine use of the chest radiograph in a child with suspected pneumonia is discouraged if the clinical presentation and management issues are straightforward.

While there are no reported studies examining clinical signs and symptoms of pneumonia and a negative chest radiograph in children, there is one report in the adult literature. A cohort of 2706 patients with clinically suspected CAP found only 1795 (66%) with radiographic confirmation of disease. Of the 34% of patients with a normal radiograph, only 7% developed a consolidation within 72 hours of presentation. There were no differences in pulmonary symptoms, laboratory testing, or mortality risk. The patients with a confirmed consolidation were more likely to have *S. pneumoniae* bacteremia (64%) compared to 14% of patients with no consolidation. Of patients with a consolidation, 92% of these were in the lower lobe and 25% also had a pleural effusion.[34] In children, the presence of tachypnea, rales, and fever suggests pneumonia, regardless of radiographic findings, but there are no well-established studies to support a diagnosis of clinical pneumonia in children. Management options may be based on clinical severity and reliability of the patient for follow-up. If a patient is only mildly ill and will reliably follow up, no antibiotic therapy is recommended. At follow-

up, a repeat radiograph may be performed or antibiotic treatment initiated if clinically indicated. If at the initial visit the patient is moderate to severely ill and/or follow-up is not guaranteed, then appropriate antibiotic therapy may be initiated based on the age of the patient and pattern of infection.

The most common impersonator of pneumonia in children is atelectasis associated with reactive airways disease, asthma, and/or bronchiolitis. Fever or markers of inflammation do not help to differentiate pneumonia, since patients with reactive airways disease may have fever and/or inflammation due to atelectasis or upper respiratory tract infection. As reported previously, wheezing is unlikely in patients with typical bacterial infections; however, atypical causes such as *M. pneumoniae* or *C. pneumoniae* should be considered. Foreign bodies may also mimic pneumonia; however, a high suspicion for aspiration or history of choking, unilateral hyperaeration, or asymmetric breath sounds may suggest the need for further investigation.[35]

The risk of bacteremia remains a consideration in children with pneumonia. In 86 patients with findings suggestive of a bacterial process (temperature > 40° C, lobar infiltrate on chest radiograph, WBC count > 20,000/mm^3 or absolute band count > 2000/mm^3, ill appearance, tachypnea, tachycardia, or otitis media), only 1 had a bacterial pathogen (*H. influenzae*) isolated by blood culture.[36] These findings are supported in additional studies with similarly low rates of bacteremia in pediatric patients with pneumonia. These studies support the lack of utility of blood cultures in patients with pneumonia, and suggest that they be reserved for the child who is toxic and/or ill appearing, is immunocompromised, has an underlying illness, or has not responded to conventional therapy.

The most common complications of pneumonia in children include necrosis, empyema, parapneumonic effusion, and lung abscess. A multicenter, retrospective study involving eight children's hospitals in the United States examined 368 hospitalized children with pneumococcal pneumonia. Of these, 133 were complicated cases and required thoracostomy drainage. The frequency of complicated cases increased during the study period from 23% in 1994 to 53% in 1999. Patients with complicated pneumonia were older (mean age 45 vs. 27 months) and more likely to be of white race and to present with chest pain. Ninety-eight percent of all patients recovered completely from the pneumonia. Antibiotic resistance was not more prevalent in the complicated patients; however, pneumococcal serotype 1 was responsible for 24% of the complicated cases and only 4% of the noncomplicated cases.[37] Pneumococcal serotype 1 is not included in the heptavalent pneumococcal conjugate vaccine, and therefore the vaccine may have a smaller impact upon the incidence of complicated pneumonia than anticipated. The issue of serotype surveillance, particularly in complicated pneumonia, remains an important component of future preventive measures.

Management

The British Thoracic Society has published an evidence-based guideline for treatment of childhood pneumonia.[38,39] Their consensus confirms a lack of good supporting evidence for management decisions. Treatment studies have small patient numbers, high recovery rates for both therapy modalities, and do not examine harm. Furthermore, the strategy to study nontreatment of a child with pneumonia is challenging.

Currently, the treatment of a child with CAP is based upon the clinical presentation and the presumed etiologic agent. Since identification of the etiologic agent remains difficult, antibiotic therapy is empirical in most cases and certainly most often in the emergency department. The reported use of antibiotics ranges from 10% to 45% to treat undifferentiated lower respiratory tract infections despite a likely viral etiology.[40-44] The issue of overuse of antibiotics is concerning, and antibiotic resistance continues to rise. Observation and close follow-up without antibiotic treatment is strongly recommended in children with a presumed viral etiology or who are relatively well appearing with only mild respiratory symptoms, as long as there is reliable follow-up.

In children who are moderately ill and/or have a presumed bacterial source of infection, antibiotics may be initiated. Since the causative pathogen is rarely known, and radiologic features do not distinguish etiology, the choice of antibiotics is based on established patterns of infection related to age and clinical findings. Several studies have found little difference in outcome when comparing different treatment modalities. One study of 88 children less than 5 years of age with pneumonia compared treatment with azithromycin and amoxicillin-clavulanate and found no difference in effectiveness. The same study compared treatment with azithromycin to erythromycin estolate in 59 children older than 5 years with pneumonia and also found no difference in outcome. Four children failed treatment, but there was no difference in failure rates among the different antibiotic regimens. Adverse events were recorded in 67% of patients who received amoxicillin-clavulanate, 25% who received erythromycin, and in 14% who received azithromycin. The most common adverse events were diarrhea and rash.[5] Another study supports the use of azithromycin for pediatric bacterial pneumonia, both classic and atypical patterns.[45] Oral azithromycin is found to be well tolerated with very few treatment-related adverse events.[46,47]

The choice of an antibiotic regimen is guided by age, severity of illness, and likelihood of a bacterial pathogen (Table 58–1).[1,5,37,39,48,49] Parenteral therapy is indicated for children who require hospitalization and who are unable to tolerate oral medication. In these cases, ampicillin or a second-generation cephalosporin (e.g., cefuroxime) is recommended. In hospitalized children 5 years and older, the addition of an oral macrolide is recommended. Replacement by an appropriate oral agent may be initiated after 2 to 4 days of clinical improvement, with resolution of fever and the ability to tolerate oral medication.[1]

Since empirical antibiotic therapy is so commonly initiated, the role for extensive microbiologic testing is of questionable value. In a prospective study of 153 hospitalized children with acquired pneumonia, only 9% had fever lasting more than 48 hours after onset of antibiotic treatment. Of these, most had RSV and *H. influenzae* infection, with more than half identified as mixed viral-bacterial etiologies. At follow-up, 94% of all patients showed no pneumonia-related symptoms. There is no role for expensive microbiologic testing in otherwise healthy children with CAP since most make a rapid, uneventful recovery after a brief hospital stay and short course of antibiotics, regardless of etiology.[50]

Table 58–1 Guidelines for Antibiotic Regimen for Community-Acquired Pneumonia in Children

Age	Most Common Bacterial Pathogen	First-Line Therapy	Second-Line Therapy
<5 yr	*Streptococcus pneumoniae*	Amoxicillin (high dose: 80–90 mg/kg/day)	Second- or third-generation cephalosporin Amoxicillin-clavulanate Macrolide*
5 yr and older	*Mycoplasma pneumoniae, Chlamydia pneumoniae*	Macrolide	Second- or third-generation cephalosporin
All ages			
	Staphylococcus aureus	Macrolide Nafcillin	Vancomycin
	Penicillin-resistant *S. pneumoniae*	Amoxicillin Amoxicillin-clavulanate	Nafcillin
Hospitalized children			
<5 yr		Ampicillin IV	Second- or third-generation cephalosporin IV
5 yr and older		Ampicillin IV Add oral or IV macrolide	Second- or third-generation cephalosporin IV Add oral or IV macrolide

*Azithromycin, clarithromycin, or erythromycin.

The heptavalent pneumococcal vaccine was introduced in 2000, and showed 97% effectiveness in reducing invasive pneumococcal disease in children less than 5 years of age based on results from the Kaiser Permanente effectiveness trial of over 36,000 children.[51] Utilizing the same patient database, the overall incidence of positive radiographic pneumococcal pneumonia in children was reported to be reduced by 18% in immunized children, with a 32% reduction in children less than 1 year of age and a 23% reduction in children less than 2 years of age. There was no difference in children older than 2 years of age.[52]

Children with the following clinical signs and symptoms should be considered for hospital admission regardless of the decision to initiate antibiotic therapy as they may require more intensive monitoring[1]: age less than 6 months, toxic appearance, severe respiratory distress, need for supplemental oxygen, dehydration, vomiting, no response to appropriate oral antimicrobial therapy, immunocompromised status, noncompliant caregiver, and presence of bilobar pneumonia.

Summary

Despite how commonly it occurs, childhood pneumonia continues to challenge the practitioner. Diagnostic testing and identification of the causative agent are limited. Routine blood tests and/or cultures are not recommended since they provide little information. Radiologic testing does not differentiate between viral and bacterial causes of pneumonia. A clinical diagnostic approach is applied for most patients, with tachypnea as the most reliable predictor of pneumonia. Wheezing suggests an atypical or viral etiology. Empirical therapy is discouraged for mildly ill children with pneumonia due to the concern for antibiotic resistance. Antimicrobial therapy is recommended for children in whom a bacterial etiology is strongly suspected or who are moderately to severely ill.

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