Pneumonia in Hospitalized Children

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Epidemiology

Pneumonia is one of the most common infections in the pediatric age group and one of the leading diagnoses that results in overnight hospital admission for children. In 2001, 198,000 patients younger than 15 years were discharged from hospitals in the United States with a primary diagnosis of pneumonia [1]. In North America, the annual incidence of pneumonia in children younger than 5 years is 30 to 45 cases per 1000; in children aged 5 years and older, the annual incidence is 16 to 22 cases per 1000 [2,3]. In developing countries, which account for more than 95% of episodes of clinical pneumonia worldwide, researchers estimate that more than 150 million new cases occur annually in children younger than 5 years [4].

Pneumonia can be classified as either community-acquired pneumonia (CAP) or nosocomial pneumonia; hospital-acquired pneumonia may be ventilator-associated pneumonia or may be acquired in the absence of mechanical ventilation. Ventilator-associated pneumonia differs in several respects from CAP and is addressed separately in this article. Although no precise definition is universally applied, CAP is generally defined as an infection of the lungs that is marked by symptoms of acute infection (ie, fever, cough, or dyspnea) and is typically associated with abnormal auscultatory findings (eg, rales or altered breath sounds) or the presence of an acute infiltrate on chest imaging in an

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individual not hospitalized or residing in a long-term care facility for at least 14 days before onset of symptoms [5].

Etiologic agents

A large number of micro-organisms can cause pneumonia in children. Table 1 lists the most frequent etiologic agents that are identified in each age group. Overall, viruses are responsible for a large percentage of cases of CAP in the pediatric age group, and they are particularly common in children aged 3 weeks to 4 years [6]. In a recent US study of children aged 2 months to 17 years who were hospitalized for pneumonia, 45% were found to have a viral etiology [7]. In general, the most frequently isolated respiratory viruses are respiratory syncytial virus, parainfluenza viruses, influenza A and B, and adenovirus, although other viruses may occur in specific settings (eg, cytomegalovirus or herpes simplex infection in neonates). Most cases of viral pneumonia can be managed without invasive diagnostic testing, and aside from supportive care, no specific antimicrobial therapy is generally required. For these reasons, the remainder of this article focuses on bacterial pneumonia, although important distinctions related to viral etiologies are highlighted when appropriate.

The epidemiology of bacterial CAP differs by age and has been impacted by vaccine strategies. From birth to 3 weeks of age, the most common causes of pneumonia are Group B streptococci and gram-negative rods (particularly enterics such as *Escherichia coli*). Although viruses predominate from 3 weeks to 3 months of age, bacterial pneumonia can occur in this age group. Afebrile pneumonia at this age is frequently caused by *Chlamydia trachomatis*; this agent

Table 1
Common causes of pediatric community-acquired pneumonia by age

Age	Etiologic agent
Birth – 3 weeks	Group B streptococcus (*Streptococcus agalactiae*)
	Gram-negative rods (eg, *Escherichia coli*)
3 wk – 3 mo	Viruses (eg, respiratory syncytial virus, parainfluenza viruses, influenza A and B, adenovirus)
	Chlamydia trachomatis
	Streptococcus pneumoniae
4 mo – 4 y	*Streptococcus pneumoniae*
	Viruses (eg, respiratory syncytial virus, parainfluenza viruses, influenza A and B, adenovirus)
	Haemophilus influenzae
	Group A streptococcus (*Streptococcus pyogenes*)
	Staphylococcus aureus
	Mycoplasma pneumoniae
	Other streptococcal species (eg, *Streptococcus milleri* group)
≥ 5 y	*Mycoplasma pneumoniae*
	Chlamydophila pneumoniae
	Streptococcus pneumoniae

rarely requires hospital admission unless found in combination with another respiratory tract pathogen, such as respiratory syncytial virus or pertussis. *Streptococcus pneumoniae* is the most common bacterial cause of febrile pneumonia among children aged 3 weeks to 4 years. A recent study from Texas found that 60% of children between 2 months and 17 years of age who were admitted with pneumonia had a bacterial pathogen isolated, and *S. pneumoniae* was confirmed in 73% of those cases [7]. Other less commonly isolated bacteria include *Haemophilus influenzae* (historically type b before widespread vaccine use, but currently includes nontypable *H. influenzae*), *Streptococcus pyogenes*, *Staphylococcus aureus*, and other streptococcal species (including the *Streptococcus milleri* group). In children aged 5 years and older, the most common bacterial pathogens are *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (previously known as *Chlamydia pneumoniae*). These atypical agents account for nearly one fourth of all cases of bacterial pneumonia among school-aged children and adolescents [7]. Pneumococcus remains high on the list of agents identified

Table 2
Less common causes of pneumonia in children

Organism	Risk factors or clinical scenarios
Human metapneumovirus	Similar in epidemiology and presentation to respiratory syncytial virus
Bordetella pertussis	Peak incidence in infants and adolescents; exposure to adults with cough illness
Mycobacterium tuberculosis	Most common cause in developing world; travel to endemic region or exposure to high-risk individuals
Listeria monocytogenes	Component of early-onset septicemia in infants from birth to 3 weeks of age; in older patients, ingestion of contaminated food or unpasteurized dairy products (disease often seen in pregnant women)
Cytomegalovirus	Infants with congenital/perinatal infection or part of disseminated illness in immunocompromised hosts
Varicella-zoster virus and herpes simplex virus	May cause pneumonia/pneumonitis as part of disseminated disease
Legionella pneumophila	Exposure to contaminated water supply
Coccidioides immitis	Travel to endemic region (southwest United States)
Histoplasma capsulatum	Travel to endemic region (Ohio and Mississippi River valley)
Blastomyces dermatitidis	Travel to endemic region (Ohio and Mississippi River valley)
Chlamydophila psittaci	Exposure to birds (parakeets)
Hantavirus	Exposure to mouse droppings
Coxiella burnetii	Exposure to sheep
Brucella abortis	Exposure to cattle or goats; ingestion of unpasteurized dairy products
Coronavirus	Associated with severe acute respiratory syndrome (SARS); travel to affected region (particularly Asia)
Avian influenza (influenza A: H5, H7, H9)	Exposure to birds; travel to affected region (Asia)
Francisella tularensis	Exposure to animals (rabbits); bioterrorist activity
Yersinia pestis	Exposure to rats; bioterrorist activity
Bacillus anthracis	Exposure to infected animals; bioterrorist activity

among children who are hospitalized for pneumonia. In addition to these common causes of pneumonia, various other micro-organisms can cause pneumonia in particular circumstances. Table 2 provides a list of these less frequent pathogens and the risk factors or clinical situations that should prompt consideration of more unusual infections. Finally, it is important to remember that a significant proportion of cases of pediatric pneumonia represents a mixed infection [8].

Pathogenesis

Pathogen, host, and environmental factors all play a role in the development of pneumonia, which typically begins with tracheal colonization by the infecting micro-organism [9]. The initial line of defense against the establishment of a respiratory pathogen is the barrier defenses of the airway, namely the mucosal barrier of respiratory epithelium and the mucociliary apparatus that is responsible for clearing foreign material and micro-organisms from the airway [10]. Once the lower respiratory tract is inoculated with a sufficient burden of bacteria, the normal inflammatory response that fights infection (which includes components such as antibodies, complement, phagocytes, and cytokines) also results in damage to functioning lung tissue [11]. The bacteria that commonly cause pneumonia also possess specific virulence factors that enhance their survival and propagation while concurrently resulting in injury to the pulmonary host. For example, *S. pneumoniae* contains pneumolysin, a pore-forming protein that enables the bacterium to kill host cells, which results in complement activation and a vigorous inflammatory response [12]. Pneumonia also may result from direct seeding of the lung tissue after bacteremia, which may be a particularly important mechanism for bacteria such as pneumococcus and *S. aureus*.

Clinical manifestations

Several studies have evaluated the use of various clinical symptoms and signs in children with pneumonia. Tachypnea widely has been shown to be the most sensitive indicator [13–16]. The World Health Organization defines tachypnea as a respiratory rate (RR) of more than 60 breaths/min in infants younger than 2 months of age, RR of more than 50 breaths/min from ages 2 to 12 months, and RR of more than 40 breaths/min in children older than 12 months [17]. Several studies have found that cutoffs of more than 50 breaths/min in children younger than 12 months and more than 40 breaths/min in children aged 12 to 35 months provide the greatest combination of sensitivity and specificity in identifying children with lower respiratory infections [18–20], although one study showed that a single value of 50 breaths/min for all ages was equally useful [21]. The precise predictive value depends on the underlying prevalence of disease [22], but a diagnosis of pneumonia in the industrialized world rarely

would be made based solely on the presence of tachypnea (which is present in many other childhood illnesses, including bronchiolitis and asthma).

Fever and cough are also frequently present in children with pneumonia, and clinical signs may include retractions or abnormal auscultatory findings, such as rales or decreased breath sounds, which tend to be more specific as indicators of lower respiratory tract infection [23–26]. Other less specific indicators that may be seen in children include malaise, emesis, abdominal pain, and chest pain (which is particularly suggestive of bacterial pneumonia as opposed to viral etiologies, especially when pleuritic in nature). Wheezing may be seen in children with bacterial pneumonia [25] but is more suggestive of bronchiolitis or viral lower respiratory tract infection.

Diagnosis

Differential diagnosis

The diagnosis of pneumonia is likely in patients who present with fever, cough, and tachypnea and who have infiltrates on chest radiography. Various other diseases can present with a similar constellation of signs and symptoms, however. The differential diagnosis may include upper respiratory tract infection, bronchiolitis, congestive heart failure, pulmonary embolism, thoracic tumors, or inflammatory disorders (such as systemic vasculitis), among other entities [27]. Table 3 reviews diseases that should be considered when infiltrates are present on chest radiography.

Table 3
Differential diagnosis of radiographic chest infiltrates

Alveolar infiltrates	Interstitial infiltrates
Infection (pneumonia)	Infection (pneumonia)
Atelectasis	Cystic fibrosis
Pulmonary edema	Bronchopulmonary dysplasia
Hyaline membrane disease	Histiocytosis
Aspiration	Collagen-vascular diseases
Hemorrhage	Sarcoidosis
Hypersensitivity reactions	Pulmonary edema
Lymphoma (Hodgkin's or non-Hodgkin's)	Hemorrhage
Leukemia	Metastatic tumors
Sarcoidosis	Irradiation
Pulmonary alveolar proteinosis	Gaucher's disease
Intralobar sequestration	Niemann-Pick disease
Pulmonary contusion	Tuberous sclerosis
Pulmonary eosinophilia	Neurofibromatosis
	Lymphangiectasia
	Interstitial pneumonitis

Laboratory studies

Several laboratory studies may be helpful in establishing a diagnosis of pneumonia in children. Leukocytosis may be present; in one study, 26% of children who presented to the emergency department with fever and a white blood cell count of more than 20,000/mm^3 were found to have occult pneumonia on chest radiography [26]. Pneumonia also has been shown to be the most common diagnosis in children with white blood cell counts of 25,000/mm^3 or more and even in children with white blood cell counts of 35,000/mm^3 or more [28]. Other inflammatory markers, such as C-reactive protein and the erythrocyte sedimentation rate, are generally elevated. One study found that patients with an elevated C-reactive protein were more likely to have pneumonia of proven or probable bacterial cause as opposed to viral or *Mycoplasma* pneumonia [29].

Cultures of the blood for bacteria traditionally have been recommended in consensus guidelines for the diagnosis and management of pneumonia, particularly when a bacterial cause is suspected [30–32]. This recommendation stems from previous work, which suggested that the rate of bacteremia in adults hospitalized for pneumonia was in the range of 10% to 30%. Several more recent studies have attempted to evaluate the use of blood cultures in the diagnosis of pneumonia, however. In these studies, the yield of blood cultures has been lower—generally ranging from 3% to 11%—and the management of pneumonia is rarely altered [33–35]. Various organisms may be detected, but *S. pneumoniae* has been the most frequently isolated pathogen in these studies. It is likely that the current rate of bacteremia will be lower because of the introduction of the pneumococcal conjugate vaccine in the routine childhood immunization schedule. With increasing resistance to antimicrobial agents and limited available data regarding the use of cultures of the blood among children with pneumonia since the widespread use of the conjugate pneumococcal vaccine, we feel that patients with disease severe enough to require hospital admission and parenteral antimicrobial therapy generally should have cultures of blood sent before therapy. Although it is uncommon to identify a pathogen, the identification of a specific organism (such as *S. pneumoniae* or *S. aureus*) and its associated antimicrobial susceptibilities can be helpful (especially in more severe cases or when pleural effusions are present).

Several other microbiologic tests can be considered as diagnostic aids. Culture of the sputum has had variable use in published studies, with yields ranging from 5% to 34% [34,36]. To be considered reliable (ie, bronchial in origin as opposed to oropharyngeal), a sputum sample should contain fewer than ten epithelial cells per low-powered field [37]. It is difficult to obtain a good sputum sample from children, who often have a nonproductive cough. In general, a valuable sample of expectorated sputum is difficult to obtain from a preschool-aged child. Although a sputum Gram stain with a single predominant organism, leukocytes, and few epithelial cells can be helpful, a negative Gram stain result never should exclude pneumonia as a possible diagnosis. Pneumococcal urinary antigen testing is generally not recommended as a diagnostic modality in

pediatric pneumonia; despite good sensitivity, the specificity of this test is low (because it is frequently positive in individuals with nasopharyngeal colonization, particularly young children) [38,39]. Viral diagnostics (either culture or antigen detection using direct fluorescent antibodies) are not necessary in most routine pneumonia cases, but they can be useful in certain circumstances (including cases that involve immunocompromised patients or to help guide infection control precautions). *Mycoplasma* infection can be identified using serology (a positive IgM is an indicator of acute infection); polymerase chain reaction testing is also available and has higher sensitivity and specificity [40], but it is rarely necessary outside of the research setting. *C. pneumoniae* may be detected rapidly by direct fluorescent antibodies from a nasopharyngeal specimen or diagnosed by serology. *Legionella* urinary antigen is the diagnostic modality of choice when *Legionella pneumophila* infection is suspected, and the test can remain positive for weeks after acute infection. It is important to remember that the urinary antigen is negative in cases that involve other species of *Legionella*. The decision to perform a skin test with purified protein derivative in patients who present with pneumonia should be based on the presence of risk factors that would increase the likelihood of tuberculosis or when specific radiographic findings suggest mycobacterial disease (such as the presence of mediastinal adenopathy).

Radiology

The diagnosis of pneumonia frequently is made or confirmed by the presence of consolidation or infiltrates on chest radiography. The presence of respiratory signs (eg, cough, tachypnea, and rales) increases the likelihood of a positive chest radiograph, and one meta-analysis suggested that infants younger than 3 months of age with a temperature of 100.5° F or higher but with no clinical findings of pulmonary disease (defined as rales, ronchi, retractions, wheezes, tachypnea, coryza, grunting, stridor, nasal flaring, or cough) do not require routine chest radiography, because the probability of a normal chest radiograph in the absence of these findings is at least 98.98% [41,42]. When chest radiographs are obtained in patients who have pneumonia, various patterns may be seen. Alveolar infiltrates are seen more frequently in bacterial pneumonia, whereas viral infection is more frequently associated with an interstitial pattern [43]. These distinctions are not universal, however, and studies have confirmed that patients with viral pneumonia can present with infiltrates that have a lobar or alveolar appearance [44]. Interobserver agreement among radiologists about the pattern of infiltrates (alveolar versus interstitial) or the presence of air bronchograms also has been demonstrated to be poor [45]. One interesting study showed that radiologists' readings of chest radiographs in febrile children aged 3 to 24 months were biased by the reading of the treating physician (when compared with radiologists who did not have access to that information) [46]. *Mycoplasma* pneumonia appears most commonly as unilateral or bilateral areas of airspace consolidation and can include reticular or nodular opacities. On high-resolution CT, ground-glass opacities, airspace consolidation, nodules, and bronchovascu-

lar thickening are common [47]. When children exhibit persistent or progressive symptoms despite seemingly adequate therapy, contrast-enhanced chest CT can be useful in detecting suppurative complications, such as empyema or necrosis, that may require further intervention [48].

Management

Admission criteria

For adults with CAP, a prediction rule (the Pneumonia Severity Index) was developed and validated to identify patients who are at low risk for death and other adverse outcomes and who might be treated successfully as outpatients [49]. A score is created using various criteria that can be assessed at initial presentation, including demographic factors (eg, age, sex, and nursing home residence), coexisting illnesses (eg, neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, and liver disease), physical examination findings (eg, mental status, RR, heart rate, blood pressure, and temperature), and laboratory and radiographic findings (eg, arterial pH, blood urea nitrogen, sodium, glucose, hematocrit, partial pressure of arterial oxygen, and pleural effusion). Patients are placed into specific risk classes to guide decisions about the need for hospitalization.

A similar tool for pediatric patients would be useful, but no such validated scoring system has been established. Although specific admission criteria for children may vary among institutions, several criteria for admission are widely used, including ill appearance or septic physiology, hypoxia that requires oxygen administration, moderate or severe respiratory distress, inability to tolerate oral fluids or medications, and social factors, such as the absence of a telephone or the inability to follow-up with a pediatrician or return to the emergency department if disease worsens. Neonates with febrile pneumonia generally should be managed as inpatients, although one field study in India suggested that infants could be treated safely in the community after the first month of life [50]. Patients with underlying conditions that could affect their clinical course adversely and children with complicated pneumonias should be admitted for initiation of therapy.

Empiric antibiotic therapy by age group

Because the most likely etiologic agents depend on the age of the child, it is logical to select initial empiric antibiotic regimens according to age. In neonates from birth to 3 weeks of age, in whom Group B streptococcus and gram-negative rods predominate, the initial coverage should be intravenous (IV) ampicillin and gentamicin in most cases; if disease is severe, a third-generation

cephalosporin (eg, cefotaxime) may be added (while continuing the ampicillin to cover *Listeria monocytogenes*, another pathogen in this age group). From age 3 weeks to 3 months, if the infant is afebrile, erythromycin (40 mg/kg/d IV divided every 6 hours) is the drug of choice for treatment of *C. trachomatis*. If fever is present or if a child seems ill, ceftriaxone (50 mg/kg/d every 24 hours) should be given. For patients aged 4 months to 4 years, when viral pneumonia (the most common cause) is suspected, no antibiotic therapy should be administered. If bacterial pneumonia is suspected, IV ampicillin (200 mg/kg/d divided every 6 hours) can be used. If the child appears ill, ceftriaxone may be chosen instead to provide broader coverage. Finally, among children aged 5 years or older, azithromycin (one dose of 10 mg/kg, followed by 5 mg/kg/d) or erythromycin can be used in routine cases to provide coverage of atypical organisms (particularly *Mycoplasma*); ampicillin may be added if there is strong evidence of a bacterial etiology, and ceftriaxone (with or without a macrolide) may be used in children who are more ill. In all ages, if features that suggest *S. aureus* are present, oxacillin or vancomycin should be added, depending on the prevalence of methicillin-resistant staphylococcus in the community [6].

Antibiotic therapy for specific pathogens

Once a specific pathogen has been identified, coverage can be narrowed accordingly. For *Chlamydia* and *Mycoplasma* infections, a macrolide (at the doses described previously) is the drug of choice. In patients with suspected pneumococcal pneumonia, therapeutic choices are driven by local antimicrobial susceptibility patterns. When *S. pneumoniae* has been recovered from an appropriate patient specimen, the antibiotic susceptibility pattern can be used to guide therapy. For isolates that are fully susceptible to penicillin (minimal inhibitory concentration < 0.1 µg/mL), ampicillin should be administered (because of its easier dosing schedule as compared with penicillin). Even for isolates with intermediate susceptibility to penicillin (minimal inhibitory concentration 0.1–1 µg/mL), high-dose ampicillin (200 mg/kg/d) provides excellent coverage. When fully nonsusceptible isolates are encountered (minimal inhibitory concentration ≥ 2 µg/mL), ceftriaxone should be used. Unlike the treatment of meningitis, vancomycin is rarely necessary in the treatment of pneumococcal pneumonia, even when a penicillin nonsusceptible strain is the etiologic agent. It should be added only if ceftriaxone resistance (defined for pneumonia as a minimal inhibitory concentration of ≥ 4 µg/mL) is demonstrated. A recent study from Spain suggested that the combination of a beta-lactam plus a macrolide may be superior to a beta-lactam alone for the treatment of pneumococcal pneumonia in adults, but no randomized trial addressing this hypothesis has been published to date [51]. When *H. influenzae* is considered a likely pathogen (such as in children with underlying lung disease), ceftriaxone or ampicillin-sulbactam is preferred rather than ampicillin because of the presence of beta-lactamase–mediated ampicillin resistance among many *H. influenzae* isolates.

The optimal length of antimicrobial therapy for the treatment of uncomplicated or complicated pneumonia has not been well established for most pathogens. There are data to suggest that a 7- to 14-day course of therapy (or a 5-day course of azithromycin) is adequate for the treatment of *C. pneumoniae* [30,52]. For pneumococcal pneumonia, treatment probably should continue until the patient has been afebrile for 72 hours, and the total duration of therapy probably should not be less than 10 to 14 days (or 5 days if using azithromycin because of its long tissue half-life). Fevers may persist for several days after initiation of appropriate therapy, which reflects the resultant inflammatory cascade and tissue damage. No good data are available to support prolonged treatment courses for patients without underlying conditions (eg, cystic fibrosis) who have uncomplicated pneumonia. Some data suggest that shorter courses of therapy may be equivalent to current standards, although more controlled studies are needed before this practice can be recommended routinely [53,54].

Clinical practice guidelines

Several groups have published practice guidelines for the management of CAP in adults [5,30,32]. No analogous clinical practice guideline for pediatric pneumonia has been accepted universally, although several suggested guidelines have been published [8,31]. Despite the differences among various recommendations, these guidelines serve as excellent compilations of the existing evidence regarding multiple aspects of the treatment of pneumonia. The differences in recommended management strategies contribute to variation in care for this diagnosis, however [55]. Published studies of adult patients with CAP have shown that adherence to a treatment guideline results in improvement in several outcomes, including lower costs, decreased length of stay, more appropriate antibiotic usage, and lower mortality rates [56–61]. Even when guidelines are used, physicians' impressions of their adherence to clinical practice guidelines do not always match their actual adherence to the recommendations contained therein, which suggests that awareness does not guarantee familiarity [62].

Bronchoscopy

The causative organism in cases of pneumonia is frequently not identified by sputum examination or blood culture. When symptoms persist despite empiric antibiotic therapy, bronchoscopy with bronchoalveolar lavage (BAL) is a diagnostic option. Several studies have shown that culture of BAL fluid in children with pneumonia can be useful in making a microbiologic diagnosis [63,64]. Although bronchoscopy is not necessary in routine cases, it should be considered when patients fail to improve with standard therapy or when concern about antibiotic resistance or unusual organisms is high and recovery of the causative agents will change management. Early bronchoscopy may be critical for immunocompromised patients, for whom the selection of empiric therapy is difficult because of the expanded list of potential causes.

Discharge criteria

No single set of criteria defining clinical stability for inpatients with pneumonia has gained widespread acceptance, which introduces variability in decisions about discharge. The combination of normalization of vital signs, ability to take oral nutrition, and clear mental status has been shown to predict a low risk of subsequent clinical deterioration among hospitalized adults with pneumonia [65]. Time to clinical stability and 30-day post-admission mortality have been suggested to be the most reliable clinically based outcome measures for CAP (along with process-of-care measures, such as admission-to-antibiotic time, proportion of patients receiving guideline-based antibiotic therapy, and percentage of patients switched from IV to oral therapy within 24 hours of reaching clinical stability) [66].

Recommended follow-up

Follow-up of children with pneumonia after discharge from the hospital should include involvement from their pediatrician or other primary care provider to ensure that clinical stability continues and that antibiotic therapy is completed as prescribed. In otherwise healthy children, follow-up radiographic studies are not necessary after a single episode of pneumonia. Consolidation on chest radiographs can persist for up to 10 weeks, regardless of clinical improvement [67]. Children with *M. pneumoniae* infection have been found to have detectable abnormalities on high-resolution CT scans more than 1 year after the episode [68]. Follow-up radiographs should be reserved for children with underlying conditions, recurrent or persistent symptoms, or recurrent episodes of pneumonia. In these cases, a period of at least 2 to 3 weeks is recommended before obtaining a follow-up radiograph [69].

Prognosis

Although rates of hospitalization for pneumonia among children have been rising, mortality rates from childhood pneumonia in the United States declined by 97% between 1939 (24,637 deaths from pneumonia) and 1996 (800 deaths) [70]. Case fatality rates (not adjusted for underlying comorbidities) from 1995 to 1997 have been estimated to be 4% in children younger than 2 years of age and 2% in children aged 2 to 17 years [71]. Although antibiotic use probably accounted for much of the decrease in mortality rates during the early part of this time period, recent declines are likely attributable in part to improved access to care for poor children [70]. Improvements in critical care medicine also may reduce mortality, which is highest in children with underlying medical conditions.

Most children who develop pneumonia do not have any long-term sequelae. Some data suggest that up to 45% of children may have symptoms of asthma

5 years after hospitalization for pneumonia, however, which may reflect either unrecognized asthma at the time of presentation with CAP or a propensity to develop asthma after CAP [72].

Complications

Pleural effusions and empyema

Parapneumonic effusions are not uncommon with pneumonia and can occur in conjunction with most etiologic agents. Whereas *S. pneumoniae* accounts for most cases with parapneumonic effusions, *S. aureus* and *S. pyogenes* are associated with particularly high rates of effusion and empyema [73]. Tuberculosis is also a common cause in geographic areas with a high prevalence of disease and should be considered in the differential diagnosis of selected patients [74]. Traditionally, the classification of such effusions as transudative versus empyema has been based on laboratory analysis of the pleural fluid. Characteristics that suggest empyema include pH less than 7.1, lactate dehydrogenase more than 1000 IU/mL, and glucose less than 40 mg/dL [75]. Additional data that may be obtained include an elevated pleural fluid white blood cell count (ie, $>50,000/mm^3$) or a positive microbiologic study (including Gram stain, culture, or other diagnostic tests, such as stains or polymerase chain reaction). Pleural fluid cell count has limited predictive value, however [76], and a positive microbiologic diagnosis is made from pleural fluid analysis in less than one third of cases [77]. CT scan findings (such as pleural thickening or enhancement, among others) have been shown to be inaccurate in predicting which effusions meet laboratory criteria for empyema [78].

Several therapeutic options are available for the management of parapneumonic effusions. Antibiotic therapy alone may result in resolution in some cases. Drainage of the fluid by thoracentesis or placement of a drainage tube (large-bore chest tube or pigtail catheter) can remove the effusion. One study found that either needle aspiration alone or catheter drainage resulted in similar complication rates and lengths of stay, but children who underwent primary aspiration without catheter placement had a higher reintervention rate than children who had catheter placement at the time of initial drainage [79]. Lower pH (especially <7.2) and presence of loculations also were independent predictors of reintervention in this study. The natural history of parapneumonic effusions follows several stages, beginning with an exudative phase, during which the fluid is free-flowing and of low cellularity. This stage is followed 24 to 48 hours later by a fibropurulent phase, during which the accumulation of fibrin and neutrophils may result in loculation. Finally, an organizing phase occurs, with fibroblast activity resulting in the formation of a "peel." Thoracoscopy with surgical débridement may be necessary when the effusion has been longstanding enough to have allowed the development of septations, which reduce the fea-

sibility of tube drainage. Surgery has been shown to reduce the length of stay for hospitalized children whose effusions were considered high grade (defined as containing sonographic evidence of organization such as fronds, septation, or loculation) [80]. In particular, video-assisted thoracoscopic surgery has been shown to have numerous advantages compared with open thoracotomy, including fewer lung resections, fewer associated blood transfusions, less postoperative analgesia, shorter length of stay, faster resolution of fever, and shorter time to removal of chest drains [81].

An alternative option for managing loculated parapneumonic effusions is the use of intrapleural fibrinolytic agents (such as tissue plasminogen activator, streptokinase, or urokinase). These agents are used when inadequate drainage is obtained after chest tube insertion. Recent reports of fibrinolytic therapy in children demonstrate that 60% to 70% of effusions in the fibropurulent phase can be drained completely and another 20% to 30% can be drained partially using the technique of daily instillation of streptokinase or urokinase through a chest tube with a dwell time of 4 hours. This technique is ineffective in draining effusions that already have reached the organizing phase, however [82,83]. Increased drainage also has been demonstrated using a 1-hour dwell of tissue plasminogen activator [84]. One randomized trial in children showed that children who received intrapleural urokinase treatment had a shorter length of stay compared with a placebo group [85]. Fibrinolytic therapy has been associated with several rare complications, including allergic reactions (particularly with streptokinase), hemorrhage, and bronchopleural fistula formation. A large, prospective, randomized trial is needed to define better several aspects of this treatment option, including precise indications, optimal dosing and duration of therapy, and complication rates.

Necrotizing pneumonia and lung abscess

Failure to improve despite appropriate antimicrobial therapy should raise the suspicion of complications, such as parenchymal necrosis or abscess. These complications may be identified on contrast-enhanced CT scan when plain films do not reveal the findings [48]. Decreased parenchymal enhancement may herald the development of cavitary necrosis and a prolonged and more intense illness [86]. Most children who develop cavitary necrosis eventually demonstrate resolution of the pulmonary abnormality on follow-up radiography, however, even in the absence of surgical intervention [87]. Interventional procedures (eg, percutaneous catheter placement) should be avoided in children with necrotizing pneumonia, because such procedures may increase the likelihood of complications, such as bronchopleural fistula formation [88].

Lung abscess is an uncommon complication that more frequently occurs in older children. Abscesses may be primary or secondary. Experts have recommended that therapy routinely should include coverage of gram-positive organisms (*S. aureus* and streptococci) and anaerobes, although gram-negative

coverage may be required in selected circumstances. Most patients can be treated medically; needle aspiration or percutaneous catheter drainage of an abscess is safe and often provides diagnostic and therapeutic value in cases that fail to resolve on antibiotic therapy alone, without the associated complication rate seen in necrotizing pneumonia [88–90]. In general, percutaneous drainage should be considered if a patient's condition worsens or when clinical status fails to improve after 72 hours of antibiotic therapy. At least 3 weeks of IV antibiotic therapy should be delivered before lobectomy is considered [91].

Topics of particular interest to hospitalists

Recurrent pneumonia

Recurrent pneumonia is generally defined as two episodes in 1 year or more than three episodes in a lifetime. Most children with recurrent pneumonia have an identifiable underlying predisposing factor. In one pediatric study, the most common of these factors was aspiration secondary to oropharyngeal muscular incoordination (eg, in cerebral palsy); other identified illnesses included immune disorders (generally related to malignancy or abnormalities of the humoral immune system, including HIV infection), congenital heart disease, asthma, congenital or acquired anatomic abnormalities (eg, tracheoesophageal fistula), gastroesophageal reflux, and sickle cell anemia [92]. Evaluation of a child with recurrent pneumonia should include a detailed history that focuses on possible indicators of these underlying illnesses combined with a targeted diagnostic evaluation that may include tests such as swallowing studies, serum immunoglobulins, HIV testing, echocardiography, pulmonary function tests, sweat testing, or radiographic studies, such as chest CT.

Hosts with compromised protective mechanisms

Mechanical ventilation

Several underlying abnormalities may result in a predisposition to the development of pneumonia. Patients with endotracheal tubes or tracheostomies are at risk of lower respiratory tract infection because aspiration of contaminated secretions from the oropharynx or stomach is enhanced by several factors, including pooling of secretions above the cuff with subsequent leak and prolonged supine positioning [9]. Intubated patients in an intensive care unit may have fever or respiratory compromise unrelated to lung infection, and distinguishing bacterial colonization in tracheal aspirates from pneumonia can be difficult. Ventilator-associated pneumonia is best identified using a combination of diagnostic modalities. In one study, 90% of ventilated children with bacterial pneumonia met one of the following three criteria: (1) bronchoscopic

protected specimen brush culture with 10^3 or more colony-forming units/mL, (2) intracellular bacteria in 1% or more of cells retrieved by BAL, (3) BAL fluid culture with 10^4 or more colony-forming units/mL [93].

Aspiration pneumonia

Patients with gastroesophageal reflux and patients who are unable to control their secretions because of neurologic impairment (underlying or drug induced) or anatomic disruption are at risk of aspiration pneumonia. Aspiration of oropharyngeal contents may produce a chemical pneumonitis, but it is frequently difficult to assess whether the introduction of oral bacteria has resulted in the establishment of a lower respiratory tract infection. Antibiotic therapy is routinely prescribed for presumed aspiration pneumonia, and the administration of either penicillin or clindamycin (which provide reasonable coverage for oral anaerobes) has been shown to be equally effective therapy for this indication [94]. In children who experience an aspiration event after hospitalization or in others in whom infection with *Pseudomonas* or other gram-negative organisms is suspected (eg, patients with cystic fibrosis), a combination agent such as ampicillin or piperacillin and a beta-lactamase inhibitor should be considered.

Immunodeficiency

Any abnormality in the host immune system may predispose a child to develop pneumonia. Some of the more common scenarios seen in hospitalized patients include malignancy (either hematologic or solid tumors), solid organ or stem cell transplant, congenital or acquired immunodeficiencies, and autoimmune disorders or immunosuppressive medications used to treat systemic illnesses. Regardless of cause, the immunocompromised host should be considered high risk for infection and merits a more aggressive diagnostic and therapeutic approach. Table 4 reviews micro-organisms that may be pathogens in immunocompromised patients with pneumonia. In particular, viral infections (especially cytomegalovirus) and fungal infections (including *Candida* and *Aspergillus*) must be considered [95] along with unusual organisms such as *Pneumocystis jaroveci* (formerly known as *Pneumocystis carinii*) or *Cryptococcus neoformans*. Results of chest radiographs in patients with neutropenia may be negative [96], although findings that suggest an infectious cause (such as nodules) may be visible on plain films [97]. Chest CT scan may demonstrate abnormalities that are not detected on routine radiograph and may help localize lesions (particularly nodules) that are amenable to biopsy to aid in diagnosis [98]. MR imaging is another alternative diagnostic modality and may be more sensitive for the detection of necrotizing pneumonia than CT scan [99]. Flexible bronchoscopy can establish a diagnosis in many cases, and several sampling methods are available. In one study of immunocompromised patients, the diagnostic yield was highest using a combination of BAL and transbronchial biopsy (70%), as compared with BAL alone (38%), transbronchial biopsy alone (38%), or protected specimen brush sampling (13%) [100]. Finally, lung biopsy may be considered to assist in making a diagnosis in patients with a concerning

Table 4
Etiologic agents of pneumonia in immunocompromised hosts

Organism	Comment
Pneumocystis jaroveci	Previously called Pneumocystis carinii; associated with cellular immune defects, including HIV infection; typically seen when CD4 count is less than 200 cells/mm^3 or in infants from 3 – 6 months of age
Cryptococcus neoformans	Yeast; intrinsically resistant to caspofungin
Candida spp	May be part of disseminated deep-organ infection
Aspergillus spp	Common cause of nodular lung infection
Zygomycetes	Family of fungi that includes Rhizopus, Mucor, and others; may be resistant to amphotericin B
Nocardia spp	Environmental bacteria; commonly cause infection of lungs, brain, or skin; require long-term therapy
Cytomegalovirus	Pneumonia as part of disseminated disease
Herpes simplex virus and varicella-zoster virus	Pneumonia as part of disseminated disease
Encapsulated bacteria (S. pneumoniae, H. influenzae, Salmonella spp)	Respiratory infections in asplenic hosts or hosts with humoral immune defects
Nosocomial bacteria, including Pseudomonas or enteric gram-negative rods	Consider as cause of pneumonia in neutropenic patients; may be seen in association with central venous catheter infections

clinical status in whom noninvasive testing has failed to uncover an etiologic agent [101]. In general, decisions regarding diagnostic testing may need to be accelerated in this population of patients to permit any interventions to be performed before clinical status deteriorates and a patient is unable to tolerate invasive procedures and to allow appropriate therapy to be initiated earlier in the course of disease.

Nosocomial agents

The differential diagnosis of pneumonia in patients who have been hospitalized for any prolonged period should include routine infectious etiologies and hospital-acquired organisms. Failure to improve with appropriate empiric therapy should raise the concern for antimicrobial resistance. Organisms of particular importance in these situations may include methicillin-resistant S. aureus, vancomycin-resistant enterococci, and gram-negative rods with resistance to third-generation cephalosporins, among others. Empiric coverage for pneumonia in patients in the intensive care unit or others at risk for nosocomial infections should include broad-spectrum agents that provide coverage for these antibiotic-resistant organisms (and any organisms known to be a frequent cause of hospital-acquired infections in the institution) until a specific diagnosis can be made and antimicrobial susceptibilities are available. The infection control staff and the hospital microbiology laboratory are invaluable resources in determining which organisms should be considered in these circumstances.

Infection control

Isolation precautions are a topic of particular interest to hospitalists who manage patients with pneumonia, particularly when a specific etiologic agent has not been identified. Because pneumonia can be caused by a wide variety of agents, several different infection control precautions may be appropriate. The single most important procedure to prevent the spread of infection in the hospital is hand hygiene (performed either with soap and water or a waterless alcohol-based hand sanitizer). Table 5 reviews the correct precautions for specific organisms that may be encountered in the hospital setting. Two infections that merit specific mention are pertussis and influenza. These organisms are highly infectious, and exposure among hospital staff may require chemoprophylaxis. Patients with pertussis or influenza should be admitted to a single room whenever possible. Staff also should wear masks when entering the room of patients with influenza (despite the fact that droplet transmission precautions usually only require masks within 3 feet), because several reports have suggested a role for airborne transmission [102–104]. When pulmonary tuberculosis is suspected, strict attention to airborne precautions must be followed. In addition to the use of respirators and negative-pressure isolation rooms, visitation should be limited when possible; at our institution, two primary visitors may undergo screening chest radiography to ensure that they do not have active pulmonary infection.

Table 5
Infection control precautions for specific organisms

Organism	Precautions[a]
Respiratory syncytial virus	Contact
Influenza	Droplet plus mask to enter room, single room
Parainfluenza	Contact
Adenovirus	Droplet and contact
Varicella	Airborne (for chickenpox, non-immune individuals should not enter room); precaution room with anteroom or single room with door closed at all times; zoster in an immunocompromised patient requires airborne and contact precautions
Mycoplasma pneumoniae	Droplet
Bordetella pertussis	Droplet (until patient has received 5 days of effective therapy)
Mycobacterium tuberculosis	Airborne; negative-pressure precaution room with anteroom
Multidrug-resistant bacteria (methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, resistant gram-negative rods)	Special organism precautions

[a] Contact refers to gown and gloves; droplet refers to mask within 3 feet; airborne refers to N95 respirator to enter room; special organism precautions refers to gown and gloves and dedicated patient equipment.

Outpatient antimicrobial therapy

As medical care for complex patients increasingly shifts from the inpatient to the outpatient arena, a greater number of infections are being treated by continuing the delivery of parenteral antibiotic therapy in the home or at step-down facilities [105–107]. Outpatient parenteral antimicrobial therapy (OPAT) is a reasonable option for patients with pneumonia who have stabilized clinically in the hospital but are judged to require prolonged parenteral treatment. The treatment of lower respiratory tract infections using OPAT has resulted in excellent clinical outcomes and high levels of patient and physician satisfaction [108,109]. Eligibility for OPAT requires a suitable home environment and the selection of an antimicrobial agent with appropriate pharmacokinetic parameters and drug stability to allow a reasonable dosing schedule at home [110]. An infectious diseases specialist (or a physician knowledgeable about the use of antimicrobial agents in OPAT) and a hospital pharmacist should be involved before discharge in planning for the administration of OPAT. The involvement of discharge planning services in the hospital also can facilitate contact with visiting nurse associations, which can arrange to instruct families in the proper techniques for IV infusions in the home. These agencies can make home visits to observe caregivers and answer questions and obtain blood for laboratory monitoring of disease or medication toxicities. The use of these services, in conjunction with careful follow-up by primary care physicians, provides the best continuity of care from the hospital to the outpatient setting and helps to ensure that patients with pneumonia receive the highest quality of care across the health care spectrum.

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