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Educational Gaps

1. The widespread use of the pneumococcal conjugate vaccine has reduced the overall incidence of pneumococcal disease, but its effect on the epidemiology of infections caused by nonvaccine serotypes and by multiply antibiotic-resistant pneumococci underscores the ongoing need for vigilance and surveillance for pneumococcal disease in the United States and worldwide.
2. According to the latest US estimates from 2012, there were 31,600 cases (10.1 per 100,000 population) and 3,300 deaths (1.1 per 100,000 population) attributable to invasive pneumococcal disease. (1)

Objectives After reading this article, readers should be able to:

1. Discuss the effect of pneumococcal conjugate vaccine use on pneumococcal disease burden.
2. Discuss the common clinical manifestations of invasive and noninvasive infections caused by *Streptococcus pneumoniae*.
3. Identify the children at high risk of pneumococcal acquisition and those at risk of poor outcome from pneumococcal infections.
4. Identify the correct antibiotics to use when treating a pneumococcal infection, using the isolate's susceptibility and the site of the infection and the antibiotic's route of administration.

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ABBREVIATIONS

AOM	acute otitis media
CSF	cerebrospinal fluid
HIV	human immunodeficiency virus
IPD	invasive pneumococcal disease
MIC	minimum inhibiting concentration
PCV	pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine

KEY POINTS

1. The prevalence of invasive pneumococcal disease is highest among children younger than 5 years and adults 65 years and older.
2. Pneumococcal conjugate vaccine use has reduced the burden of invasive and noninvasive pneumococcal infections; however, there is a constant need for surveillance for pneumococcal disease caused by nonvaccine serotypes.
3. Polymerase chain reaction–based testing can detect *Streptococcus pneumoniae* DNA in clinical samples and is an emerging tool for improving the microbiologic diagnosis of pneumococcal disease.

4. Treatment of pneumococcal infections with effective antimicrobials greatly improves the outcome. The route of antibiotic administration (oral or parenteral) should be based on the severity of the illness and the host's risk of serious morbidity or mortality.
5. Definitive therapy should be driven by results of antibiotic susceptibility testing of the isolated pneumococcus and tailored according to the complexity and site of infection (ie, bacteremia vs meningitis), route of antimicrobial administration, and characteristics of the infected host (ie, healthy vs immunosuppressed).

INTRODUCTION

Streptococcus pneumoniae (commonly referred to as pneumococcus) is a major cause of serious illness and death worldwide. The World Health Organization estimates that 735,000 global pneumococcal deaths and 14.5 million global pneumococcal cases per year occurred in children (uninfected with human immunodeficiency virus [HIV]) younger than 5 years in 2000. The biggest burden of pneumococcal childhood infections is in children living in the developing world, especially in India, Nigeria, Ethiopia, Democratic Republic of Congo, Afghanistan, and China. Cases from these regions accounted for more than half of all pneumococcal deaths in children younger than 5 years in 2000.

In the United States and other industrialized countries, pneumococcal infections continue to pose significant challenges for clinicians, even more than a decade since the introduction of pneumococcal conjugate vaccines (PCVs). The routine use of a 7-valent (4, 6B, 9V, 14, 18C, 19F, and 23F) PCV (PCV7) in infants and children was followed by a significant reduction in overall invasive and respiratory pneumococcal infections. Nevertheless, according to the latest US estimates from 2012, the rate of invasive pneumococcal disease (IPD) was 10.1 cases and 1.1 deaths per 100,000 persons. (1) In addition, a shift to infections caused by nonvaccine serotypes was noted, which has prompted the inclusion of 6 additional serotypes in the vaccine (1, 3, 5, 6A, 7F, and 19A) to produce a 13-valent PCV (PCV13). (2)

Further complicating the management of pneumococcal infections has been the worldwide emergence of multiply antibiotic-resistant pneumococci. Continued vigilance and monitoring of the epidemiology of pneumococcal infections in children and adults are required to better understand the disease burden and effect of vaccination on these infections.

MICROBIOLOGY AND PATHOGENESIS

S pneumoniae is a gram-positive, catalase-negative, facultative anaerobe that produces α-hemolysis on blood agar. The pneumococcus has 90 distinct serotypes based on their capsular polysaccharide. These serotypes may be grouped together based on antigenic similarities. Within each serogroup, pneumococcal serotypes may have immunologic cross-reactivity, which may result in some cross-protection. However, no such cross-reactivity exists among serotypes in different serogroups.

Pneumococci avidly adhere to the epithelial cells of the nasopharynx of healthy children without causing symptoms. Colonization with a pneumococcal serotype, however, does not produce immunity against reacquisition of that serotype. On the other hand, pneumococcal disease (local or invasive) is usually followed by a serotype-specific humoral immunity in a healthy host that protects against recurrent infection by the same serotype. Children may carry various pneumococcal serotypes at different times, and a recent acquisition of a new serotype, in the absence of serotype-specific humoral immunity, is believed to precede an upper respiratory tract or invasive infection by that pneumococcus. Serotypes vary in their ability to colonize the nasopharynx and their virulence to cause disease. In fact, certain pneumococcal serotypes are infrequently isolated from the nasopharynx of carriers but are disproportionately responsible for invasive infections.

On entering the bloodstream of the host, the pneumococcal capsule helps the bacterium evade phagocytosis and complement-mediated bactericidal activity. In the respiratory tract, pneumococci can proliferate and evade clearance by pulmonary macrophages, especially in the setting of biologic (eg, viral coinfection) or mechanical (eg, aspiration) disrupting factors.

EPIDEMIOLOGY

Pneumococcal disease can occur at any age; however, the incidence of invasive disease attributable to *S pneumoniae* is highest in children younger than 5 years and in elderly populations. Pneumococcal carriage is common and more likely to occur in infancy and early childhood. Rates of nasopharyngeal colonization vary by age, geography, and population studied. Risk factors for pneumococcal carriage include age younger than 2 years (especially infants), attendance at out-of-home child care, exposure to overcrowding and household smoking, winter season, and lack of breastfeeding (despite the fact that protective factors in human milk have yet to be identified). (3) Among adults, those living in households with young children are more likely to be

colonized with pneumococcus in their nasopharynx than adults without such exposure (a twofold higher colonization rate in one population study from Virginia). (4)

A child's risk of IPD is increased in the presence of certain underlying medical conditions or demographic factors. These factors include age younger than 2 years (especially between ages 6 and 11 months), minority groups (eg, African American, Alaskan Native, or Native American), low-income household, out-of-home child care, sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, HIV, and cochlear implants (particularly implants with a positioner component). Other conditions that increase the risk of IPD include cerebrospinal fluid (CSF) leakage, immunosuppressive states (eg, congenital immunodeficiency of humoral [B-cell], T-cell, complement, or phagocytic disorders [excluding chronic granulomatous disease], malignant tumor, or chemotherapy, radiation, or medication-induced conditions), chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic pulmonary disease, chronic renal disease (especially nephrotic syndrome), and diabetes mellitus. These risk factors also increase the risk of recurrent pneumococcal disease.

Pneumococcal disease is mostly episodic; however, transmission from person to person via respiratory droplets may lead to outbreaks and case clusters in overcrowded settings, such as military barracks. Pneumococcal infections are more common during the winter and in early spring when respiratory diseases are more common.

Effect of PCVs

Non-IPD mainly presents as an acute infection of the upper (otitis media or sinusitis) or lower (pneumonia) respiratory tract. *S pneumoniae* remains the leading cause of acute otitis media (AOM) and acute bacterial sinusitis followed by *Haemophilus influenzae, Moraxella catarrhalis,* and other bacteria. The widespread use of PCV7 in the United States since 2000 was followed by a modest reduction in all cases of AOM in children with a relative increase in disease caused by other bacterial causes, as well as replacement of pneumococcal serotypes with those not included in the vaccine. Children receiving PCV7 were also found to have fewer recurrences of AOM and reduced need for placement of tympanostomy tubes.

The reduction in nasal colonization rates as a result of PCV use has led to a decrease in IPD, AOM, acute bacterial sinusitis, and pneumonia caused by *S pneumoniae* serotypes represented in the vaccine. In children younger than 2 years, IPD was reduced by 60% to 90% after the widespread use of PCV7. The largest decreases were noted in children ages 12 to 23 months who had the highest prevaccination era rates (82% reduction from 205 to 37 cases per 100,000 population), followed by children younger than 12 months. (5) In the same age group, studies have found that PCV7 use reduced the incidence of any-cause pneumonia substantially (ranging from 26% to 57%) compared with the prevaccination era. However, there were reports of an increase in cases of pneumococcal empyema attributed mainly to serotype 19A, a serotype not included in PCV7. Similarly, pneumococcal meningitis cases decreased with the widespread use of PCV7, a reduction of 65% among children younger than 2 years.

In the years after the introduction of PCV7, the incidence of IPD in children younger than 5 years decreased from 95 cases per 100,000 US population in 1999 to 22 to 25 cases per 100,000 population in 2002 and have continued to decrease. According to provisional data presented in the Active Bacterial Core Surveillance Report from 2012, issued by the Emerging Infections Program Network at the Centers for Disease Control and Prevention, the incidence of IPD has decreased to 9 per 100,000 persons younger than 5 years. The full report is available on the Internet at http://www.cdc.gov/abcs/reports-findings/survreports/spneu12.html.

However, an increase in non-PCV7 serotypes causing IPD (from 17% in 1998-1999 to 98% in 2006-2007) partially offset these reductions. In fact, *S pneumoniae* has the ability to undergo genetic transformation (ie, switching its polysaccharide capsule to a different type) in response to selective pressure, such as that exerted by PCVs. This capsular switching is partly responsible for the increase in pneumococcal disease caused by nonvaccine serotypes. The inclusion of 6 additional serotypes in PCV13 and its introduction in the US since 2010 have the potential to further reduce IPD among children younger than 5 years. Ongoing postlicensure monitoring is crucial to help characterize the effectiveness of PCV13 in different populations and track the potential changes in disease burden caused by non-PCV13 serotypes.

The reduction in pneumococcal nasopharyngeal carriage, invasive and noninvasive disease was also noticed in unvaccinated children and adults, albeit to a lesser extent than in vaccinated ones. This finding is likely attributed to an indirect herd effect due to reduced transmission of pneumococcal serotypes contained in the PCV7. Similar effects are expected to persist with the use of PCV13. The potential herd effect of the conjugate vaccine on pneumococcal carriage and disease is serotype specific. For instance, serotypes 1 and 5 in PCV13 are rarely found to colonize the nasopharynx as opposed to serotype 19A, which is also

included in PCV13 but has a high affinity to colonize the nasopharynx. Thus, the effect of the vaccine on disease caused by these serotypes will vary and need to be tracked further in the years after routine use of PCV13.

S pneumoniae are a major cause of bacteremia (frequently presenting as fever without a localizing source) and bacterial meningitis in unvaccinated children. The introduction of PCV7 has led to a 70% to 90% reduction in bacteremia and IPD.

There is also evidence of a herd effect, a modest reduction of disease caused by nonvaccine strains, and a decrease in antibiotic resistance among strains that cause disease. (6) After PCV use, rates of pneumococcal meningitis have similarly decreased. Pathogens (eg, *Neisseria meningitides* and *Escherichia coli*) not prominently encountered before pneumococcal vaccination are relatively increasingly identified. In addition, serotypes of *S pneumoniae* not included in the vaccines have also assumed a more prominent etiologic role as they replaced vaccine serotypes in children's nasopharynx.

The rates of pneumococcal disease attributed to antibiotic-resistant strains have decreased, correlating with the overall decrease in pneumococcal disease after the use of PCV7. (7) Reports indicate that the decrease was greatest for IPD among young (81% decrease in those younger than 2 years) followed by elderly (49% decrease in those age ≥65 years) populations. The least effect was seen for non-IPD (ie, a modest or no change for antibiotic-resistant pneumococcal AOM).

CLINICAL MANIFESTATIONS

Pneumococci are a major cause of childhood infections. Infection is predominantly of the respiratory tract (AOM, sinusitis, and pneumonia); however, invasive disease may occur in the form of bacteremia, sepsis, meningitis, or other organ systems involvement (eg, osteoarticular infection, peritonitis, or hemolytic uremic syndrome). The spectrum of severity can vary from mild to life-threatening in healthy and immunocompromised hosts alike. Prompt diagnosis, antimicrobial use, and supportive therapy have greatly reduced the morbidity and mortality of pneumococcal childhood infections.

Upper Respiratory Tract Infection

Pneumococcal infection of the upper respiratory tract may not be easily differentiated from that caused by *Haemophilus*, *Moraxella*, or other respiratory pathogens. However, pneumococcal AOM is less likely to resolve spontaneously and is usually associated with more severe disease. It predominantly affects infants and preschool children, peaking between ages 6 and 18 months, and may cause recurrent infections in certain vulnerable populations. The diagnosis of AOM is usually made clinically based on history and physical examination findings of middle ear effusion and inflammation. A definitive etiologic diagnosis (eg, organism isolation by tympanocentesis) is rarely required apart from the settings of complicated otitis or research. Children with acute bacterial sinusitis are similarly diagnosed according to clinical history and physical examination. Acute bacterial sinusitis is usually caused by the same respiratory pathogens encountered in AOM.

Pneumonia

Although more than two-thirds of cases of childhood pneumonia beyond the neonatal period are viral, pneumococcus remains an important cause of bacterial community-acquired pneumonia among young children. Its clinical presentation may be indistinguishable from other causes of pneumonia but with an increased likelihood of high temperatures, shaking chills, prominent cough, and dyspnea accompanied by lower respiratory tract signs of distress (such as tachypnea and retractions), decreased air entry, and crepitations (crackles or rales) on chest auscultation. Infants and younger children may have less specific respiratory symptoms and frequently present with vomiting and abdominal pain or distention. Children with pneumococcal pneumonia may have a mild to moderate parapneumonic effusion, a necrotizing pneumonia, or an empyema that requires evacuation. Concomitant bacteremia at the time of presentation may be identified in 20% to 30% of cases.

Most cases of childhood pneumonia are managed empirically without identifying a definitive cause. In more complicated cases, culture of lower respiratory tract secretions acquired by bronchoalveolar lavage or of pleural fluid drained surgically or by paracentesis may help guide therapeutic decisions. Culture of expectorated sputum and rapid antigen tests performed on pharyngeal specimens have not proven to be clinically useful (poorly sensitive and specific) for diagnosing pneumococcal pneumonia in children.

Invasive Pneumococcal Disease

Pneumococcal bacteremia in a febrile child without a localizing focus after history, physical examination, and laboratory investigations is an important presentation of IPD. It has become uncommon in children immunized with PCV (incidence is now estimated to be approximately 0.5%) but may still be seen in the unimmunized or when IPD is caused by nonvaccine serotypes. Almost all cases of pneumococcal bacteremia are benign, transient, and self-limited

events. Affected children may appear relatively well and have a mild to moderate illness course. However, they could also present acutely with abrupt severe illness, sepsis, purpura, disseminated coagulopathy, and progression to shock and multiorgan failure, especially in the setting of asplenia or sickle cell disease. Prompt supportive and definitive therapy may greatly improve the short- and long-term outcome of these children.

Meningitis is one of the most serious invasive infections caused by *S pneumoniae*. Along with *N meningitides*, pneumococci are the most common bacteria to cause childhood meningitis beyond the neonatal period since the widespread use of the *H influenzae* type b conjugate vaccine. Classic manifestations include fever, nuchal rigidity, headache, or altered mental status. Infants may present with irritability, a bulging fontanelle, and seizures, whereas vomiting and focal neurologic signs are more prominent in older children. The infection may cause a rapid progression to obtundation, coma, and death within 24 hours of illness onset. The definitive diagnosis is commonly (>90%) made by isolating the organism from CSF acquired by lumbar puncture. Characteristically, there is neutrophilic pleocytosis, a low CSF–serum glucose ratio (<0.6), and an elevated protein level. With prompt antibiotic therapy and other supportive measures, the morbidity and mortality from pneumococcal meningitis may be reduced significantly. Poor prognosis may be predicted by the presence of a low CSF glucose, altered mental status, and shock at presentation. Currently, fatality rates in infected children are less than 10%; however, long-term neurologic sequelae (eg, sensorineural hearing loss, seizures, and motor or cognitive deficits) may still be noted in 20% to 50% of survivors. (8)(9)(10)

Among clinical entities worthy of special mention is pneumococcal peritonitis, which occurs mostly in children with nephrotic syndrome who are also at increased risk of other forms of IPD due to their hypogammaglobulinemic state. Other less common pneumococcal invasive infections in children include osteoarticular infection, endocarditis, soft tissue infection (eg, periorbital cellulitis), and hemolytic uremic syndrome.

DIAGNOSIS

A definitive diagnosis of pneumococcal infection is usually attained by isolating the organism in culture from blood or normally sterile body fluid, tissue, or site (eg, pleural fluid, CSF, synovial fluid, or cardiac vegetation). The bacterium typically grows within 24 hours. In cases of uncomplicated noninvasive pneumococcal infection, such as AOM, sinusitis, or pneumonia, the diagnosis is clinical, and isolation of the organism is difficult and not routinely justified for management.

Gram staining of specimens that reveals the presence of gram-positive diplococci may provide a quick suggestion of a pneumococcal cause. Other rapid antigen detection tests, such as enzyme immunoassay or latex agglutination tests, are poorly sensitive and not specific enough to be of clinical value. An immunochromatic test for detection of pneumococcal antigen in urine or CSF of individuals with pneumococcal pneumonia or meningitis, respectively, has shown some promise in adults. However, the test is not clinically useful in children because of the confounding state of pneumococcal nasopharyngeal colonization in childhood, which leads to an unacceptably high rate of false-positive results.

Real-time polymerase chain reaction–based techniques may be used to identify *S pneumoniae* in clinical specimens and may also be used for serotyping isolates. These assays have the advantage of detecting both viable and nonviable *S pneumoniae* in these clinical samples.

MANAGEMENT

Pneumococci can alter their cell wall penicillin-binding proteins and become resistant to penicillins. Since the 1990's, pneumococcal strains that are also resistant to cephalosporins (including the commonly used third-generation ceftriaxone and cefotaxime) and other β-lactams have been identified increasingly all over the world. Pneumococcal resistance has also been described against macrolides (erythromycin, clarithromycin, or azithromycin), trimethoprim-sulfamethoxazole, clindamycin, rifampin, and fluoroquinolones. Penicillin-resistant isolates are more likely than susceptible isolates to have a high level of resistance to additional classes of antimicrobials. Surveillance programs in the United States have reported rates of resistance to trimethoprim-sulfamethoxazole and erythromycin, reaching 92% and 61%, respectively, among highly penicillin-resistant pneumococci and remaining at 6.6% and 3.2%, respectively, among the penicillin-susceptible pneumococci. Most of the penicillin-resistant pneumococci remain susceptible to carbapenems (eg, meropenem), rifampin, and the fluoroquinolone levofloxacin, whereas resistance to clindamycin may reach 12% to 15%. On the other hand, vancomycin remains an effective antibiotic for treating *S pneumoniae*, and no vancomycin resistance has been identified. Other newly developed antimicrobial agents, including the oxazolidinone linezolid and the lipopeptide daptomycin, have also been used effectively to

TABLE 1. **Clinical and Laboratory Standards Institute's New Minimum Inhibiting Concentration (MIC) Susceptibility Breakpoints for Pneumococci by Clinical Syndrome and Route of Administration**

	MIC, μG/ML		
	SUSCEPTIBLE	NONSUSCEPTIBLE	
ANTIBIOTIC, ROUTE, AND SITE		INTERMEDIATE	RESISTANT
Intravenous penicillin			
Meningitis	<0.06		≥0.12
Nonmeningitis	<2.0	4.0	≥8.0
Oral penicillin			
Nonmeningitis	<0.06	0.12-1	≥2.0
Intravenous ceftriaxone or cefotaxime			
Meningitis	<0.5	1.0	≥2.0
Nonmeningitis	≤1.0	2.0	≥4.0

treat infections caused by multiply antibiotic-resistant *S pneumoniae*.

When β-lactams are delivered to a site of pneumococcal infection in sufficiently high levels, nonsusceptible (ie, intermediate and resistant) strains may still be effectively eradicated. Pneumococcal infections at sites where high antibiotic local concentrations are difficult to attain, such as the case with meningitis, would be an exception. In 2008, on the basis of accumulated clinical experience and pharmacokinetic and pharmacodynamic data, the Clinical and Laboratory Standards Institute released new interpretive definitions of susceptibility breakpoints for pneumococci to various antibiotics by clinical syndrome and administered route. As indicated in Table 1, the minimum inhibiting concentration (MIC) cutoff at which a pneumococcus isolate is considered nonsusceptible is lower for patients with meningitis than for patients without meningitis. In addition, the susceptibility breakpoint will depend on whether the antibiotic is administered parenterally or orally.

The recommended dosing regimens for preferred and alternative antibiotic agents used to treat select childhood pneumococcal infections are listed in Table 2 and discussed in the following sections.

Respiratory Tract Infection

High-dose amoxicillin (80-90 mg/kg per day) remains the recommended treatment for uncomplicated AOM (when the decision to treat with antibiotics has been made), acute bacterial sinusitis, and pneumonia. (11)(12) The recommended length of therapy for uncomplicated AOM is 7 to 10 days (may be as short as 5 days in children older than 5 years). Children with acute bacterial sinusitis may require a longer duration of therapy of 10 to 14 days if symptoms have not resolved. In case of amoxicillin treatment failure within 2 to 3 days or for the child who has received amoxicillin within the past 30 days, has a concurrent purulent conjunctivitis, or has a history of recurrent AOM unresponsive to amoxicillin, second-line agents may be used that have better activity against β-lactamase–producing *H influenzae* or *M catarrhalis*. These agents include amoxicillin-clavulanate (in a 14:1 composition ratio; 80-90 mg/kg per day of the amoxicillin component divided in 2 doses), cefdinir (14 mg/kg per day divided every 12 to 24 hours), cefuroxime (30 mg/kg per day divided every 12 hours), cefpodoxime (10 mg/kg per day divided every 12 hours) or ceftriaxone (50 mg/kg, administered intramuscularly). Clindamycin (20-40 mg/kg per day divided every 8 hours) may be of benefit when penicillin-resistant pneumococci are suspected: however, the drug may not be effective against multidrug-resistant *S pneumoniae*. When patients have an allergic hypersensitivity reaction to penicillins and to cephalosporins, a macrolide (azithromycin or clarithromycin) may be indicated.

Mild to moderate community-acquired pneumonia, suspected to be bacterial in origin, occurring in previously healthy, fully immunized infants and children should be treated with oral amoxicillin (90 mg/kg per day in 2 doses or

TABLE 2. **Recommended Dosing Regimens of Preferred and Alternative Antibiotic Agents Used in Treating Select Childhood Pneumococcal Infections**

	ANTIBIOTIC	
PNEUMOCOCCAL INFECTION	**PREFERRED**	**ALTERNATIVE**
AOM[a] or sinusitis	Amoxicillin (90 mg/kg per day in 2 doses or 45 mg/kg per day in 3 doses)	Amoxicillin-clavulanate (14:1 composition, 80-90[b] mg/kg per day in 2 doses), cefdinir (14 mg/kg per day in 1-2 doses), cefuroxime (30 mg/kg per day in 2 doses), cefpodoxime (10 mg/kg per day in 2 doses), ceftriaxone (50 mg/kg intramuscularly), or clindamycin[c] (30 mg/kg per day in 3 doses)
Pneumonia		
Streptococcus pneumoniae with MIC to penicillin ≤2 μg/mL[d]		
Oral route	Amoxicillin (90 mg/kg per day in 2 doses or 45 mg/kg per day in 3 doses)	A second- or third-generation cephalosporin (see above) or levofloxacin if susceptible (16-20 mg/kg per day in 2 doses for ages 6 months to 5 years or 8-10 mg/kg per day in 1 dose for ages 5-16 years[e]) or linezolid (30 mg/kg per day in 3 doses for ages <12 years or 20 mg/kg per day in 2 doses for ages ≥12 years)
Parenteral route	Ampicillin (200 mg/kg per day every 6 hours) or penicillin (250-400 U/kg per day every 4-6 hours)	Ceftriaxone (75-100 mg/kg per day every 12-24 hours or cefotaxime (150 mg/kg per day every 8 hours) or clindamycin[c] (40 mg/kg per day every 6-8 hours), or vancomycin (40-60 mg/kg per day every 6-8 hours)
S pneumoniae with MIC to penicillin ≥4 μg/mL[d]		
Oral route	Levofloxacin if susceptible (16-20 mg/kg per day in 2 doses for ages 6 months to 5 years or 8-10 mg/kg per day in 1 dose for ages 5 to 16 years[e]) or linezolid (30 mg/kg per day in 3 doses for ages <12 years or 20 mg/kg per day in 2 doses for ages ≥12 years)	Clindamycin[c] (30-40 mg/kg per day in 3 doses)
Parenteral route	Ceftriaxone (100 mg/kg per day every 12-24 hours)	Ampicillin (400 mg/kg per day every 6 hours) or levofloxacin if susceptible (16-20 mg/kg per day in 2 doses for ages 6 months to 5 years or 8-10 mg/kg per day in 1 dose for ages 5 to 16 years[e]) or linezolid (30 mg/kg per day in 3 doses for ages <12 years or 20 mg/kg per day in 2 doses for ages ≥12 years). Others: clindamycin[c] (40 mg/kg per day every 6-8 hours) or vancomycin (40-60 mg/kg per day every 6-8 hours)
Meningitis		
Empiric therapy	Vancomycin (60 mg/kg per day every 6-8 hours) PLUS ceftriaxone (100 mg/kg per day every 12-24 hours) or cefotaxime 150 mg/kg per day every 6-8 hours)	
Penicillin-susceptible *S pneumoniae* (MIC <0.06 μg/mL)	Penicillin G (250-400 U/kg per day every 4-6 hours)	Ceftriaxone or cefotaxime alone (same dose as for empiric)
Penicillin-nonsusceptible (MIC ≥0.12 μg/mL), cephalosporin-susceptible (MIC <0.5 μg/mL) *S pneumoniae*	Ceftriaxone (100 mg/kg per day every 12-24 hours)	Cefotaxime

Continued

TABLE 2. (Continued)

	ANTIBIOTIC	
PNEUMOCOCCAL INFECTION	PREFERRED	ALTERNATIVE
Penicillin-nonsusceptible (MIC ≥0.12 μg/mL), cephalosporin-nonsusceptible (MIC >0.5 μg/mL) *S pneumoniae*	Vancomycin (60 mg/kg per day every 6-8 hours) plus ceftriaxone (100 mg/kg per day every 12-24 hours)	Cefotaxime (high dose) may be used in place of ceftriaxone (see text). Rifampin (20 mg/kg per day in 2 doses may be added; see text)

[a]*For full details refer to Lieberthal et al. (11)*
[b]*Dose based on amoxicillin component.*
[c]*Clindamycin resistance among* Streptococcus pneumoniae *has been increasing and varies geographically.*
[d]*For full details refer to Bradley et al. (12)*
[e]*Levofloxacin maximum daily dose is 750 mg.*

45 mg/kg per day in 3 doses). A macrolide antibiotic may be empirically added in school-aged children and adolescents when atypical agents of pneumonia (eg, *Mycoplasma* or *Chlamydophila*) are suspected.

Children with complicated pneumococcal otitis or sinusitis and those with severe pneumonia requiring hospitalization may be treated with parenteral penicillin G (250,000-400,000 U/kg per day divided every 4-6 hours) or ampicillin (up to 400 mg/kg per day divided every 6 hours). A parenteral third-generation cephalosporin (eg, ceftriaxone [75-100 mg/kg per day divided every 12-24 hours] or cefotaxime [150 mg/kg per day divided every 8 hours]) may be substituted in the setting of an unimmunized child, a complicating empyema, or when there is high local prevalence of penicillin-resistant *S pneumoniae* in the community. Alternative agents, such as vancomycin (40-60 mg/kg per day divided every 6-8 hours), clindamycin, levofloxacin, or linezolid, should only be considered when patients cannot tolerate the β-lactams or when the *S pneumoniae* isolate is highly resistant to ceftriaxone or cefotaxime (eg, MIC ≥4 μg/mL) where clinical failures have been described.

Bacteremia

Occult pneumococcal bacteremia has become uncommon in well-appearing, immunized children ages 3 to 36 months who present with fever without an identifiable focus of infection. Nevertheless, uncomplicated bacteremia in these children may be treated with a parenteral or a high-dose oral β-lactam agent if close follow-up evaluation is assured.

Meningitis

Empiric antibiotic therapy for childhood meningitis should include ceftriaxone (100 mg/kg per day divided every 12 hours) or cefotaxime (300 mg/kg per day divided every 6-8 hours) plus vancomycin (60 mg/kg per day divided every 6 hours). Vancomycin is added because of the fear of multiply antibiotic-resistant pneumococci. This empiric therapy is also adequately effective against *N meningitides* and the occasional *H influenzae* type b that causes meningitis.

Therapy may be modified once the organism is identified and the susceptibility profile is determined. If *S pneumoniae* is found to be susceptible to penicillin, use of vancomycin should be discontinued, and the patient may be treated with either penicillin G (250,000-400,000 U/kg per day in 4-6 divided daily doses) or ceftriaxone or cefotaxime alone. If the *S pneumoniae* is nonsusceptible to penicillin but susceptible to ceftriaxone and cefotaxime, then treatment with either cephalosporin alone for at least 10 days is sufficient.

If a pneumococcus-causing meningitis is found to be nonsusceptible to penicillin and to the cephalosporins, then the treatment should be continued with vancomycin and the third-generation cephalosporin. The cephalosporin treatment is continued to account for the unreliable penetration of vancomycin into the CSF and because the cephalosporin may still be active against the isolate despite the elevated MIC. In addition, some experts would administer a higher-than-usual meningitic dose of cefotaxime to patients with pneumococcal meningitis caused by cefotaxime-nonsusceptible strains. This combination is thought to achieve more rapid elimination of the organism than vancomycin alone (data derived only from rabbit model). If the patient fails to improve, then adding rifampin (20 mg/kg per day in 2 divided doses) should also be considered if the isolate is rifampin-susceptible.

In cases of nonsusceptible pneumococcal meningitis, it is recommended to document sterility of the CSF acquired by a subsequent lumbar puncture a few days into proper antibiotic therapy.

Corticosteroid use in pneumococcal meningitis in childhood is controversial. Although supported by more evidence in adults than in children, in *H influenzae* meningitis than pneumococcal meningitis, and in high-income rather than low-income countries, use of adjunctive corticosteroids may be

effective against severe hearing loss after meningitis. Nevertheless, many reviews have found no improved survival among children with bacterial meningitis who receive corticosteroids.

The administration of corticosteroids (in the form of dexamethasone) may decrease the permeability of the inflamed blood brain barrier to vancomycin, reducing its concentration at the site of infection and potentially delaying eradication of the organism. Thus, the American Academy of Pediatrics recommends considering the use of dexamethasone in the initial therapeutic regimen for childhood pneumococcal meningitis after weighing the risks and benefits for each individual case. When used in this setting, dexamethasone treatment (0.15 mg/kg per dose every 6 hours for 48 hours) should be initiated just before or concomitant with the first dose of antibiotics. A subsequent lumbar puncture should be considered at 24 to 48 hours of therapy if dexamethasone is used (as the host's febrile response may become suppressed).

Prognosis

In healthy hosts without an underlying immune dysfunction, the early use of appropriate antibiotic therapy has reduced the mortality from pneumococcal meningitis to less than 10%. However, even with proper therapy, approximately one-third of children with pneumococcal meningitis can have severe hearing impairment, and one-fourth may have mild to profound intellectual or motor deficits. (10)(13)

PREVENTION

Prevention of Spread

Pneumococci are transmitted from person to person by respiratory droplets. In hospitalized children with invasive pneumococcal infections, standard precautions are recommended even when the isolates are antibiotic resistant. Chemoprophylaxis is not indicated for contacts of patients with IPD because secondary cases are uncommon.

Active Immunization

A 23-valent pneumococcal polysaccharide (PPSV23) has been licensed and used in adults and children older than 2 years in the United States for more than 25 years. It provides serotype-specific immunity in recipients; however, unlike conjugate vaccines, it does not induce immunologic memory or boosting with subsequent doses, it does not reduce nasopharyngeal carriage, and it does not provide indirect protection of the unimmunized. Most importantly, the serologic response to the polysaccharide antigens is poor in children younger than 2 years. This is because the capsular polysaccharides are T-independent immunogens and, therefore, have limited antibody response in young children.

Despite the advent of the conjugate vaccine, the use of PPSV23 is still indicated for children at increased risk of IPD, such as those with sickle cell disease or HIV infection, after they receive their PCV series.

PCV13 has been licensed in the United States since 2010. It contains purified capsular polysaccharides of pneumococcal serotypes 1, 3, 5, 6A, 7F, and 19A, which were added to the 7 serotypes originally included in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F). The capsular polysaccharides are then individually covalently bound to a protein carrier (a mutant diphtheria toxin). This covalent bonding with a carrier protein enables the polysaccharide antigen to be recognized by T cells and macrophages, resulting in T-dependent immunity. The role of the conjugated protein is to drive T cells to induce isotype switching and formation of memory by polysaccharide-specific B cells. Therefore, PCV13 is immunogenic in younger children and elicits immunologic memory.

PCV13 is recommended as part of the universal infant immunization schedule in the United States to be administered for all infants and children at 2, 4, and 6 months of age, with a booster between ages 12 and 15 months. Catch-up immunization with PCV13 is also recommended for all children 59 months or younger (full schedule is available in the 2012 *Red Book*).

A single PCV13 supplemental dose is recommended for children fully vaccinated with PCV7 who are healthy (up to age 59 months) or who have an underlying high-risk medical condition (up to age 71 months).

For those children ages 6 to 18 years with high-risk conditions, PCV13 may be administered regardless of whether they received PPSV23 or PCV7 previously. If PCV13 and PPSV23 are being administered, then PPSV23 should follow PCV13 administration by at least an interval of 8 weeks. In addition, a second and final dose of PPSV23 should be administered in the high-risk individuals 5 years after the initial PPSV23 dose.

Children undergoing an elective splenectomy or cochlear implant placement should receive PCV13 at least 2 weeks before the procedure. PPSV23 is also recommended for these children; however, it should be administered at least 8 weeks after PCV13 administration. PCV13 may be concurrently given with other vaccines except for meningococcal conjugate vaccine, which may interfere with PCV13 if administered concomitantly or within 4 weeks.

Antibiotic Prophylaxis

In addition to immunization, antibiotic prophylaxis with twice daily penicillin V or G (125 mg per dose for those younger than 5 years and 250 mg per dose for those 5 years or older) is recommended for children at high risk of IPD due to anatomical or functional asplenia (eg, sickle cell

disease). Prophylaxis has been found to reduce the incidence of IPD in children with sickle cell disease by 80% in a randomized controlled trial performed before the PCV7 era. Penicillin prophylaxis is usually administered until age 5 years or longer (not supported by evidence). Parents of children receiving penicillin need to still be aware that this prophylaxis may not necessarily prevent all IPD, particularly IPD that is caused by penicillin-resistant strains. Extending antibiotic prophylaxis beyond age 5 years or its administration to children with other forms of splenic dysfunction is not agreed on and has not been studied rigorously. Children with penicillin allergy may receive erythromycin as an alternative agent for prophylaxis.

Passive Immunoprophylaxis

Passive immunoprophylaxis against pneumococcal infections with the administration of intravenous immune globulin at 400 mg/kg every 4 weeks is recommended for children infected with HIV who have humoral immunodeficiency and who develop recurrent serious bacterial infections despite receiving antimicrobial prophylaxis.

Summary

- Overwhelmingly consistent evidence from observational studies has demonstrated that the pneumococcal conjugate vaccine has reduced the burden of pneumococcal disease but continues to affect the epidemiology of pneumococcal infections caused by nonvaccine serotypes and antibiotic-resistant pneumococci. (5) (6)
- On the basis of strong evidence, susceptible pneumococci causing uncomplicated, noninvasive childhood infections (eg, otitis or pneumonia) should be treated with a narrow-spectrum antimicrobial (eg, amoxicillin). (11)(12) Severely ill patients and those with infections caused by resistant pneumococci may be treated with parenteral antibiotic agents based on the isolate's susceptibility and the site of the infection.

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PIR Quiz

1. You are asked to the emergency department to see a previously healthy 1-year-old child with a temperature of 104.5°F (40.3°C), irritability, and vomiting. On physical examination, he resists active motion of his neck and seems to be holding his head very still. A complete blood cell count reveals a total white blood cell count of 21,000/μL (21 $\times$ 10^9/L) with a differential of 80% segmented neutrophils and 10% bands. You suspect bacterial meningitis. Your BEST course of action at this time is immediate empiric administration of:
   A. Ceftriaxone and ampicillin.
   B. Rifampin and ampicillin.
   C. Cefdinir and azithromycin.
   D. Vancomycin and amoxicillin.
   E. Ceftriaxone and vancomycin.
2. The mother of a 12-year-old child who has a history of invasive *Streptococcus pneumoniae* disease insists that her child had received all the appropriate vaccines for his age, including the 7-valent pneumococcal conjugate vaccine (PCV7). She wants to know why her child was infected with *S pneumoniae*. Of the following, the MOST likely reason for the patient's illness was:
   A. The child likely missed a vaccine dose of PCV7.
   B. The child was likely infected with a PCV strain not included in the PCV7 vaccine.
   C. The child was likely infected with a *Haemophilus influenza* not *S pneumoniae*.
   D. The child likely has an underlying medical condition that made him more susceptible to *S pneumoniae* infection.
   E. The child was likely colonized in his nasopharynx with a large microbial burden of *S pneumoniae*.
3. In discussing the benefits of the 13-valent pneumococcal conjugate vaccine (PCV13) with the parents of a young infant, the father tells you that he read about the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and wants to know why PPSV23 is not used for young infants because it contains protection again more serotypes. Of the following, the BEST response is:
   A. PPSV23 does not cover pneumococcal strains that infect children younger than 2 years.
   B. PPSV23 only reduces nasopharyngeal carriage of *S pneumoniae*.
   C. The child will also need to receive PPSV23 vaccination after age 2 years.
   D. The serologic response to the polysaccharide antigens is poor in children younger than 2 years.
   E. PPSV23 is only recommended in children who are human immunodeficiency virus positive.
4. You are seeing a 6-year-old child in your office with a history of low-grade fevers, cough, and purulent rhinorrhea for 5 days. He has also had a mild frontal headache. He is non–toxic-appearing but is febrile with a temperature of 100.8°F (38.2°C). His lungs are clear to auscultation, and heart sounds are normal. He has enlarged and erythematous nasal turbinates, with thick yellow nasal discharge. You make the diagnosis of acute bacterial sinusitis. Of the following, the next BEST step in management is:
   A. Treat with amoxicillin (80-90 mg/kg per day) for 10 to 14 days.
   B. Treat with amoxicillin-clavulanate (50 mg/kg per day of an amoxicillin component) for 7 to 10 days.
   C. Treat with clindamycin (20-40 mg/kg per day) for 7 to 10 days.
   D. Treat with azithromycin (10 mg/kg per day) for 10 to 14 days.
   E. Treat with cefdinir (14 mg/kg per day) for 7 to 10 days.
5. A 13-year-old boy comes to see you as a new patient to your office. He has a history of sickle cell disease and mild intermittent asthma. He has had several hospitalizations in the past for sickle cell pain crises. Currently, he is feeling well and has no symptoms. He did not

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at http://pedsinreview.org.

To successfully complete 2014 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

receive PCV7 or PCV13 but received PPSV23 at ages 3 and 8 years. His other vaccinations are up to date. What is the next BEST step in management at this time?

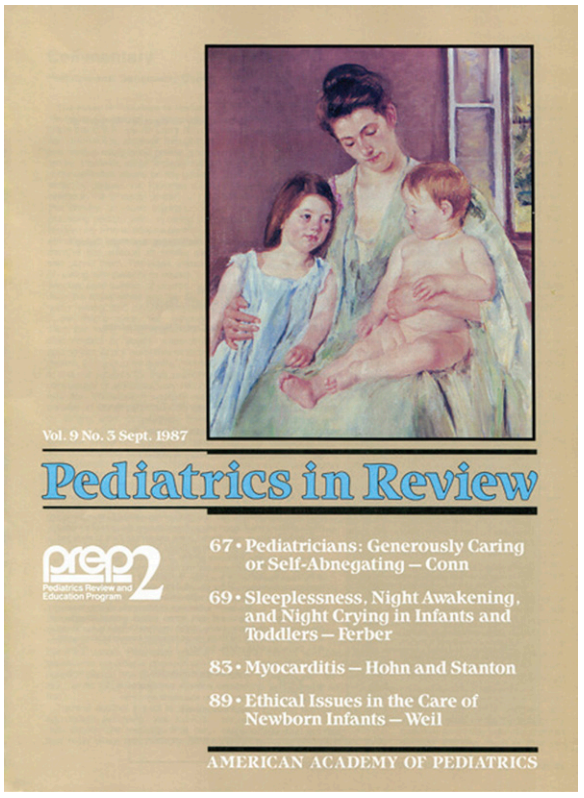
A. No vaccinations are indicated at this time.
B. Administration of PCV13.
C. Administration of PCV7.
D. Administration of PPSV23.
E. Administration of both PPSV23 and PCV13.

In Memoriam

Although Dr Robert J. Haggerty is the founding editor of *Pediatrics in Review* (*PIR*), the journal had an energetic, engaging cofounder, his wife of 64 years, Muriel E. Haggerty. Trained as an obstetrics nurse, Mrs Haggerty accompanied her husband on many of his pediatric endeavors, offering sage advice, social support, and affectionate insight. American Academy of Pediatrics (AAP) Executive Director Dr Errol Alden, in a 2004 article in *AAP News*, was quoted as saying that Bob and Muriel Haggerty "literally put [PIR] together out of their apartment" and that although Bob was the sole editor, Muriel was the assistant. Although both Bob and Muriel were involved with the journal *Pediatrics* for a while, to them, from 1979 on, *PIR* was a labor of love.

In May of this year, Muriel passed away. Part of her legacy was her love of art, which she shared for years with the readers of *PIR*. Unbeknownst to many of us on the editorial board, she and Bob combed the nation's art museums for portraits of children for the cover of *PIR*. We are all grateful for Muriel's gracious hand in the raising of *PIR*.

–*J.Z.*



Mrs. Muriel Haggerty is shown with her husband, Dr. Robert J. Haggerty, at a 2004 event recognizing his years of service to the Academy and his retirement as editor in chief of *Pediatrics in Review*.

Pneumococcal Infections

Nizar F. Maraqa

Pediatrics in Review 2014;35;299
DOI: 10.1542/pir.35-7-299

Pediatrics. Dr Nagan, a resident from Boston University School of Medicine and Harvard Medical School Pediatric Residency Program, wrote this case report. Choosing which case to publish involved considerations of the teaching value and excellence of writing, but also the content needs of the journal. Another case will be chosen from the finalists presented at this year's AAP National Conference and Exhibition and published in the September 2015 issue of Pediatrics in Review.

To view Suggested Reading lists for these cases, visit https://pedsinreview.aappublications.org and click on the "Index of Suspicion" link.

Parent Resources from the AAP at HealthyChildren.org

Case 4:

- English: http://www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/Celiac-Disease.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/abdominal/Paginas/Celiac-Disease.aspx

Corrections

In the July Pediatrics in Review article "Pneumococcal Infections" (Maraq N. Peds in Rev. 2014;35(7):299–310, doi: 10.1542/pir.35-7-299), there is an error on page 301, column 2, line 2. The parenthetical phrase should read: " ... (82% reduction from 205 to 37 cases per 100,000 population ... "). The journal regrets the error.

The June 2014 article "Influenza and Parainfluenza Viral Infections" (Fox TG and Christenson JC. *Pediatrics in Review.* 2014;35(6):217–228, doi: 10.1542/pir.35-6-217) contained an abbreviation error on p. 22, column 2, lines 6 and 9. The abbreviation "IIA" should be "IIV." The sentences should read: "Several studies have found superior efficacy of LAIV compared with IIV. (21) In children 6 years or older and adolescents with asthma, the LAIV provided a 32% increase in protection against culture-proven influenza infections when compared with IIV. (22)" The journal regrets the error.

ANSWER KEY for September 2014 PEDIATRICS IN REVIEW:

Knee Conditions: 1. A; 2. B; 3. B; 4. A; 5. C.

Managing Adolescent Gynecology: 1. D; 2. B; 3. D; 4. E; 5. D.

Tobacco in the 21st Century: 1. D; 2. B; 3. A; 4. D; 5. A.