

Pneumococcal Infections

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

1. Discuss the common clinical presentations of pneumococcal infections.
2. Describe the resistance patterns of *Streptococcus pneumoniae* and the usual recommendations for therapy of pneumococcal infections.
3. Characterize the treatment of pneumococcal meningitis.
4. Delineate the differences between the two licensed pneumococcal vaccines and the indications for their administration.
5. Describe the impact of the conjugate pneumococcal vaccine on pneumococcal infection in the United States.

Introduction

With the successful control of *Haemophilus influenzae* invasive disease in the United States following the introduction of vaccine in the 1990s, attention has turned increasingly to *Streptococcus pneumoniae*, the leading bacterial cause of respiratory tract infections. At least 1 million children, mostly in developing countries, die each year from pneumococcal disease. It is the most important cause of otitis media, which in the United States accounts for more than 16 million medical visits per year. Prior to the introduction of pneumococcal immunization in the United States, *S pneumoniae* was responsible for 500,000 cases of pneumonia, 60,000 cases of bacteremia, 3,000 cases of meningitis, and 200 childhood deaths yearly.

Until the 20th century, invasive pneumococcal infection usually had a fatal outcome. The introduction of antibiotics in the mid-20th century was a major advance, but the development of pneumococcal antibiotic resistance late in the century has led to major therapeutic problems. Nonetheless, we have come a long way in the management of pneumococcal infection since the early days of the 20th century when serotherapy was employed. House officers in Boston, with their patient's pneumococcal isolate in hand, travelled by trolley to Dr Maxwell Finland's laboratory at the Boston City Hospital to have the organism serotyped and then be handed the corresponding serum to take back to administer to the patient.

Epidemiology

Pneumococci are part of the normal upper respiratory tract flora in healthy children and are spread person-to-person by large droplets. Virtually all children become colonized, and 25% to 75% of infants carry pneumococci at any given time. The highest colonization rates occur in young babies, boys, children who reside in institutions, and children who attend child care centers. Other risk factors for colonization include absence of breastfeeding, viral upper respiratory tract infection, passive exposure to cigarette smoke, and having older siblings who attend child care. Nasopharyngeal carriage of pneumococcus is a prerequisite for invasive disease; acquisition of a new strain of pneumococcus is associated with a 15% risk of developing infection (eg, otitis media). The risk of colonization with antibiotic-resistant *S pneumoniae* correlates with age younger than 2 years, child care attendance, and recent antibiotic administration (≤ 3 mo). Children colonized with resistant strains are more likely to have unresolved acute otitis media. Risk factors for developing pneumococcal disease include specific ethnic backgrounds (African-American, Native American, Alaskan Eskimos) and underlying diseases, including antibody deficiency syndromes,

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Table 1. Risk Factors for Pneumococcal Infection

- Age younger than 2 y
- Exposure to child care, overcrowding, smoke, bottle-feeding
- Ethnic background: African-American, Native American, Alaskan Eskimo
- Viral respiratory tract infection
- Underlying illness (at risk for invasive disease)
 - Splenic dysfunction or absence (eg, sickle cell disease, asplenia, surgical splenectomy)
 - Human immunodeficiency virus disease
 - Antibody deficiency syndrome/other immunodeficiency
 - Malignancy
 - Nephrotic syndrome/chronic renal insufficiency
 - Chronic cardiac or pulmonary disease (excluding asthma)
 - Cerebrospinal fluid leaks
 - Diabetes
 - Cochlear implant

human immunodeficiency virus disease, complement disorders, splenic dysfunction, malignancy, and nephrotic syndrome (Table 1).

Pathogenesis

S pneumoniae is a gram-positive organism that grows on blood agar. On Gram stain it may appear as a single coccus, as diplococci identifiable because of a lancet shape, and as chains of variable length. Anaerobic conditions and carbon dioxide enhance growth. Colonies on blood agar are alpha-hemolytic. More than 90 serotypes have been identified to date. A polysaccharide capsule surrounds the cell wall and is the major antigenic component of the organism. Pneumococcal virulence is determined by the quantity of polysaccharide produced, by the specific composition of the capsule, and by other cell wall carbohydrates and cell surface proteins, including pneumolysin, a protein that is toxic to a wide variety of cells.

Host defense against pneumococcal infections begins at the mucosal barrier, with entrapment in the mucus blanket and killing by lysozyme and other enzymes. Alpha-lactalbumin in human milk is active against pneumococci and may provide protection to nursing infants. Opsonization, phagocytosis, and killing of pneumococci are facilitated by type-specific antibodies directed against the capsular polysaccharide. The development of natural type-specific immunity to polysaccharide antigens such as the pneumococcal capsule is T-cell-independent,

Table 2. Common Sites of Pneumococcal Infection

Localized Disease

- Otitis media
- Sinusitis
- Pneumonia
- Conjunctivitis

Invasive Disease

- Bacteremia/sepsis
- Meningitis
- Septic arthritis/osteomyelitis
- Complicated pneumonia/empyema

which results in an immune response that is short-lived and does not induce an anamnestic (booster) response upon re-exposure to the polysaccharide. Children younger than 2 years of age respond poorly to T-cell-independent antigens and have poor humoral immune response to polysaccharides, whether from natural infection or pneumococcal polysaccharide vaccine. Thus, the 23-valent pneumococcal polysaccharide vaccine available since the 1980s does not reduce nasopharyngeal colonization and does not protect children younger than 2 years of age reliably.

Clinical Aspects

S pneumoniae is primarily a respiratory tract pathogen (Table 2). The most common disease caused by the pneumococcus is acute otitis media, an illness that affects infants and young children, with a peak incidence in the 6- to 18-month age group. It is manifested clinically by the acute onset of symptoms and signs of middle ear inflammation (eg, otalgia) in association with otoscopic findings of middle ear effusion. Two thirds of children in the United States have had an episode of otitis media by the time they are 1 year old, and more than 80% by the time they are 3 years old. It is the most common reason for children to be brought for medical care, representing approximately 25% of pediatric visits and more than 20 million visits per year. Approximately 500,000 tympanostomy tubes are placed yearly in the United States for middle ear disease. The pneumococcus causes 30% to 50% of cases of acute otitis media (with *H influenzae* representing 15% to 30% of cases and *Moraxella catarrhalis* representing about 5% to 15% of cases). A history and physical examination do not distinguish which children have which pathogen, although children who have pneumococcal disease tend to have more severe

infection. Pneumococcal otitis media is the least likely to resolve spontaneously without antibiotic intervention.

Sinusitis is caused by the same pathogens as acute otitis media, with pneumococcus being the most important. Children who have acute sinusitis may present with facial pain, fever, and purulent nasal discharge or simply with persistent rhinorrhea, day- and nighttime cough, and malodorous breath. The pneumococcus also is a common bacterial cause of conjunctivitis, clinically manifested by conjunctival injection and purulent drainage.

Pneumonia represents the other major respiratory tract infection commonly caused by the pneumococcus. *S pneumoniae* accounts for up to one quarter to one third of all cases. The clinical presentation for pneumococcal pneumonia varies substantially and overlaps with the presentation of pneumonia caused by other pathogens, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and respiratory viruses. Children who have pneumococcal pneumonia may be very ill, with high fever, cough, and tachypnea. Findings on examination may include diminished breath sounds and crackles as well as consolidation on chest radiography. Complications such as empyema occur rarely. Some children who have pneumococcal pneumonia may have milder illness, with a more protracted course and less impressive signs.

Meningitis is the most serious form of invasive pneumococcal infection, and *S pneumoniae* is one of the two most important causes of this infection in the United States (the other being *Neisseria meningitidis*). Disease can be fulminant, with onset of symptoms to obtundation within 24 hours, or it can be very gradual, with children developing the typical signs or symptoms (headache, fever, vomiting, and lethargy) over several days before the diagnosis is made. Despite appropriate antibiotic therapy and supportive care, neurologic sequelae may develop in 25% to 50% of survivors, and the condition occasionally is fatal. The most common sequela is sensorineural hearing loss, but significant motor or cognitive impairment may be seen.

Other serious pneumococcal infections include hematogenous osteomyelitis and septic arthritis. The femur and humerus are the bones affected most commonly, with knee and hip joints typically involved. Another invasive infection, pneumococcal bacteremia, occurs in the first 2 to 3 years of life; affected children present with high fevers, often in the context of a respiratory illness. They generally have no findings on physical examination to identify a focus of infection (such as otitis or pneumonia), but leukocytosis almost always is found. Other serious but less common pneumococcal infections in-

clude endocarditis, soft-tissue infections, pericarditis, peritonitis, and neonatal sepsis.

Pneumococcal infection is diagnosed by Gram stain and culture of appropriate specimens (eg, from blood and suppurative foci). Rapid antigen detection methods generally are not very sensitive or specific and are not very useful clinically. Susceptibility testing should be carried out on all isolates. Recovery of pneumococci from a pharyngeal or nasal swab does not indicate specifically that it is the cause of otitis, sinusitis, or pneumonia; such cultures usually are not recommended.

Treatment

Over the past 15 years, an increasing proportion of *S pneumoniae* strains worldwide have been shown not to be susceptible to penicillin and ampicillin, to the third-generation cephalosporins cefotaxime and ceftriaxone, and to a number of other agents, including erythromycin, macrolides, and trimethoprim-sulfamethoxazole. In some parts of the United States, as many as 40% or more of strains are penicillin-nonsusceptible, with about 50% of these being intermediately susceptible and 50% being fully resistant. Resistance is caused by altered penicillin-binding proteins. In general, the susceptibility of the pneumococcus to other beta-lactam antibiotics (eg, third-generation cephalosporins) decreases in parallel to decreasing penicillin susceptibility. Thus, approximately 50% of penicillin-nonsusceptible strains also are not susceptible to cefotaxime and ceftriaxone. Penicillin-nonsusceptible strains also have increased rates of resistance to erythromycin, macrolides, clindamycin, and trimethoprim-sulfamethoxazole.

It is important to recognize that beta-lactam antibiotics generally are clinically effective in treating these nonsusceptible strains if sufficient doses are provided to maintain adequate drug concentrations at the site of infection. Thus, except for meningitis, pneumococcal infections, even when caused by resistant strains, usually can be treated successfully with full doses of beta-lactam antibiotics.

Based on the previously noted considerations, bacterial meningitis proven or suspected to be caused by *S pneumoniae* should be treated initially with a combination of vancomycin and ceftriaxone or cefotaxime (Table 3). (For children who cannot receive cephalosporins due to a serious cephalosporin or penicillin allergy [eg, anaphylaxis], rifampin should be added to the vancomycin regimen.) Once susceptibility testing results are available, vancomycin generally may be discontinued, unless the organism is found to be nonsusceptible to both penicillin and to cefotaxime/ceftriaxone. In such cases, the cep-

Table 3. Parenteral Antibiotic Therapy for Pneumococcal Meningitis

Drug	Daily Dose per kg	Interval
Penicillin	400,000 U	4 to 6 h
Ampicillin	300 to 400 mg	4 to 6 h
Ceftriaxone	100 mg	12 to 24 h
Cefotaxime	300 mg	8 h
Vancomycin	60 mg	6 h
Meropenem	120 mg	8 h
Rifampin	20 mg	12 h

alosporin usually is continued nonetheless because of the better experience with beta-lactam agents in treating meningitis and unreliable central nervous system penetration of vancomycin. Other agents that may be considered based on susceptibility testing are meropenem and chloramphenicol. Dexamethasone often is added as adjunctive therapy, although unlike the experience with *H influenzae* type b meningitis, data are insufficient to demonstrate a clear benefit for children who have pneumococcal meningitis.

Penicillin, ampicillin, cefotaxime, or ceftriaxone are used routinely for nonmeningeal invasive pneumococcal infections (Table 4). Patients in whom nonsusceptible strains of pneumococcus are isolated respond as well to these agents as do patients who have susceptible strains, and vancomycin generally is not recommended or necessary. Other potentially useful agents include clindamycin, meropenem, and imipenem.

For treatment of otitis media, high-dose oral amoxicillin at a dose of 80 to 90 mg/kg per day divided BID is recommended (Table 5). On the basis of achievable middle ear concentration and in vitro activity, no other oral beta-lactam agent has better activity than amoxicillin against nonsusceptible *S pneumoniae* strains. Therapy

Table 4. Parenteral Antibiotic Therapy for Invasive Pneumococcal Disease (Nonmeningitis)

Drug	Daily Dose per kg	Interval
Penicillin	250,000 to 300,000 U	4 to 6 h
Ampicillin	100 to 200 mg	6 h
Ceftriaxone	50 mg	24 h
Cefotaxime	100 mg	8 h
Vancomycin	40 mg	6 h
Clindamycin	30 to 40 mg	6 to 8 h

may be shortened to 5 days, particularly in older children. For patients who have penicillin allergy as well as those who have clinically defined treatment failure (assessed 3 to 5 d after initial therapy), alternative agents include cefdinir, cefuroxime axetil, and cefpodoxime. High-dose oral amoxicillin/clavulanate (14:1 formulation) may be used (80 to 90 mg/kg per day of the amoxicillin component) to achieve better activity against *H influenzae* and *M catarrhalis*, but this agent has no more activity against the pneumococcus than does amoxicillin because resistance to penicillin and amoxicillin is not mediated by beta-lactamase production. Clindamycin also may be considered for treatment of pneumococcal otitis media, although it is not active against *H influenzae* or *M catarrhalis*. Macrolide drugs such as erythromycin, clarithromycin, and azithromycin are potential alternatives, especially for penicillin-allergic patients, but resistance to these agents among pneumococcal isolates runs as high as 30% and cannot be overcome by increasing the dose. Similarly, 30% to 40% of pneumococci are resistant to trimethoprim-sulfamethoxazole, precluding its use as a first-line choice for acute otitis media.

Treatment of sinusitis is similar to that for otitis media because the pathogens are the same. The management of pneumonia in childhood is more complex because although *S pneumoniae* remains the most important bacterial cause in all age groups, other potentially treatable organisms such as *M pneumoniae* and *Chlamydia pneumoniae* play important roles. For a young infant in whom the most important treatable pathogen is the pneumococcus, management is similar to that for otitis media. For an older school-age child, depending on other clinical and epidemiologic features, regimens directed at the other pathogens often are warranted.

Pneumococcal Vaccination

Two pneumococcal vaccines are available for use in children in the United States (Table 6). In 2000 the heptavalent pneumococcal conjugate vaccine (PCV7) was introduced into the childhood immunization schedule. In this conjugate vaccine, the polysaccharide capsule is linked to a mutant diphtheria protein, which renders the immune response to be T-cell-dependent. This vaccine is immunogenic in the first months after birth and is associated with high levels of antibody, durable humoral production, and an anamnestic response following subsequent challenges. The vaccine contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, which account for more than 80% of cases of bacteremia and meningitis and more than 70% of cases of pneumococcal otitis media in United States children younger than 6 years of age. In

Table 5. Oral Antibiotic Therapy for Noninvasive Pneumococcal Infections

Drug	Daily Dose per kg	Interval
Amoxicillin	80 to 90 mg	8 to 12 h
Amoxicillin–clavulanate (14/1)	80 to 90 mg	8 to 12 h
Cefpodoxime proxetil	10 mg	12 h
Cefdinir	14 mg	12 to 24 h
Cefuroxime axetil	30 mg	12 h
Clindamycin	20 to 40 mg	8 h

addition, 80% of penicillin-nonsusceptible strains of pneumococcus are represented by these same seven serotypes.

PCV7 is administered as part of a four-dose series to all children in conjunction with the other routine childhood vaccines and is administered at 2, 4, 6, and 12 to 15 months of age. Children who do not receive PCV7 in the first 2 years of life and who are younger than age 5 years also may be immunized with PCV7 in accordance with American Academy of Pediatrics recommendations, as outlined in the *Red Book*. Specifically, children who have underlying illness (Table 1) should receive vaccine, as should children who live in crowded housing, attend out-of-home child care, are exposed to cigarette smoke, or have histories of recurrent otitis media. Immunocompetent children receive only one dose; children who are immunocompromised (sickle cell disease, splenic dysfunction, human immunodeficiency virus [HIV] disease, malignancy) should receive two doses administered 2 months apart, followed by one dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23) administered 2 months after the second dose of PCV7.

PPV23 is not reliably immunogenic in infants younger than age 2 years and is not administered routinely to older healthy children. However, it is recommended starting at age 2 years for children at highest risk of invasive pneumococcal infection, including those who have sickle cell disease, congenital or acquired asplenia, splenic dysfunction, and HIV disease. Other children at increased risk for invasive pneumococcal disease who should receive PPV23 at age 2 (following immunization in the first 2 years of life with PCV7) are listed in Table 1. Children in the aforementioned highest risk group should receive repeat doses of PPV23 every 3 to 5 years. Children who have sickle cell dis-

ease also should receive antibiotic prophylaxis at least up to age 5 years, generally with penicillin or amoxicillin. Children who have other forms of asplenia also should receive antibiotics through age 5 years and, in some instances, may benefit from prophylaxis throughout childhood.

Data on the impact of pneumococcal vaccine in preventing invasive disease are impressive (Table

7). In the precensure studies of more than 37,000 infants from northern California, only one child in the vaccine recipient group developed invasive disease compared with 39 in the control group, yielding a 97% efficacy in protection against vaccine serotypes, with no corresponding increase in invasive disease caused by non-vaccine serotypes in the vaccine group. More recent studies continue to show a major reduction in invasive disease among vaccine recipients without a sizable increase in disease caused by “replacement” nonvaccine serotypes. Importantly, these studies also demonstrate a reduction in disease among individuals who were not vaccine recipients (“community or herd immunity”). For example, in one national study, young adults (ages 20 to 39 y) experienced a 32% reduction in invasive pneumococcal disease following the introduction of childhood PCV, with older age groups also experiencing declines, but of a lesser magnitude.

Further, clinically diagnosed pneumonia in the California study was reduced in vaccine recipients by 4.3%. In the subgroup of children who had pneumonia and had radiographs taken, significant findings (peripheral infiltrates/consolidation/empyema) were reduced by 20.5% among children who had received the pneumococcal vaccine. In a more recent South African study, vaccine recipients experienced a 25% reduction in radiologically confirmed consolidation.

Studies to date have shown a more modest reduction

Table 6. Comparison of Pneumococcal Vaccines

	PCV7 (Conjugate)	PPV23 (Polysaccharide)
Serotypes	7	23
Thymic recruitment	T-cell-dependent	T-cell-independent
Immunogenic in those younger than age 2 y	Yes	No
Anamnestic (booster) response	Yes	No
Durable immune response	Yes	No

Table 7. Impact of PCV7

Clinical Event	Result
Invasive disease	~90% reduction
Invasive disease in contacts	~25% reduction
Pneumonia	~10% reduction
Otitis media	~5% to 10% reduction
Antibiotic courses	~5% to 10% reduction

in cases of acute otitis media among vaccine recipients. In a Finnish study, acute otitis media episodes were reduced by 6%, with a 34% reduction in acute otitis media caused by pneumococci of any serotype and a 57% reduction of culture-confirmed cases by vaccine serotypes. However, there was a 33% increase in the rate of acute otitis media caused by nonvaccine pneumococcal serotypes as well as an increase in cases caused by *H influenzae*. A follow-up study demonstrated a 39% reduction in tympanostomy tube placements among children who received the vaccine. Likewise, in the northern California studies, there was a 23% reduction of tympanostomy tube placement in the children who received the pneumococcal vaccine, with the incidence of otitis media in vaccine recipients reduced by 8% and antibiotic courses reduced by 6%.

Several studies have shown that immunization reduces nasopharyngeal carriage of vaccine serotypes up to as much as 50%. Isolation of antibiotic-resistant pneumococci from these children also is reduced because vaccine serotypes are the most likely to be nonsusceptible. However, isolation of nonvaccine serotypes in vaccine recipients was increased, resulting in no overall major change in carriage of the pneumococcus.

Prior to the introduction of pneumococcal immunization, vaccine strains were carried frequently and recurrently by infants; they induced poor antibody response and tended to cause prolonged disease, with the development of resistance due to extended antibiotic exposure. The impact of the vaccine has been to reduce carriage of resistant strains and decrease invasive disease dramatically. Although replacement disease (especially otitis media) clearly is occurring, it appears to be limited

and usually is caused by less resistant pneumococcal strains as well as by *H influenzae*. To date, replacement disease is not significant enough to outweigh the benefits of pneumococcal vaccination.

Future approaches include expansion of the seven-valent vaccine to include more serotypes. New approaches to immunization using DNA or protein antigens common to all pneumococcal serotypes offer obvious potential advantages.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

5. Adequate antibody responses to 23-valent pneumococcal polysaccharide vaccine do not occur until children are:
 - A. 6 months old.
 - B. 12 months old.
 - C. 18 months old.
 - D. 2 years old.
 - E. 3 years old.

6. The most common disease caused by *Streptococcus pneumoniae* is:
 - A. Acute otitis media.
 - B. Conjunctivitis.
 - C. Meningitis.
 - D. Pneumonia.
 - E. Sinusitis.

7. Among the following, the drug of choice for a child who has acute otitis media due to nonsusceptible pneumococcus is:
 - A. Amoxicillin.
 - B. Amoxicillin/clavulanate.
 - C. Clindamycin.
 - D. Erythromycin.
 - E. Trimethoprim-sulfamethoxazole.

8. Among the following, the drug of choice for a child who has sinusitis due to nonsusceptible pneumococcus is:
 - A. Amoxicillin.
 - B. Amoxicillin/clavulanate.
 - C. Clindamycin.
 - D. Erythromycin.
 - E. Trimethoprim-sulfamethoxazole.

9. With the introduction of pneumococcal vaccine, the overall carriage of pneumococci in the nasopharynx of children has:
 - A. Decreased by 25%.
 - B. Decreased by 50%.
 - C. Increased by 25%.
 - D. Increased by 50%.
 - E. Remained unchanged.