Strategies in the treatment of penicillin-resistant Streptococcus pneumoniae

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Abstract: The epidemiology, resistance mechanisms, susceptibility testing, treatment, prevention, and clinical importance of penicillin-resistant Streptococcus pneumoniae (PRSP) infection are discussed.

PRSP is an established presence in the United States, with some geographic areas reporting decreased susceptibility in up to half of isolates. The mechanism of resistance to β-lactam antibiotics in S. pneumoniae is genetic changes resulting in decreased binding of drug to the bacterial cell wall. Emerging PRSP strains have necessitated testing as a tool in selecting drugs for treating life-threatening infections. Opinions differ on how to treat these infections empirically. Non-life-threatening infections, such as otitis media, are still often treated successfully with amoxicillin, amoxicillin–clavulanate potassium, or a third-generation cephalosporin. Currently recommended initial treatment of pneumococcal pneumonia in otherwise healthy patients requiring hospitalization consists of cefuroxime, ceftriaxone, or cefotaxime; some authors continue to emphasize injectable penicillin. Once the mainstay of empirical treatment of pneumococcal meningitis, penicillin has largely been abandoned in favor of cefotaxime or ceftriaxone. Vaccination remains an underutilized strategy in at-risk populations. The clinical importance of penicillin resistance among pneumococci is still uncertain.

Changing patterns in the susceptibility of S. pneumoniae to penicillin make selection of appropriate therapy increasingly difficult. Key considerations are the site of infection and the level of resistance.

Index terms: Antibiotics; Drugs; Epidemiology; Immunization; Penicillin; Penicillins; Pneumococcal infections; Pneumococcal vaccines; Resistance; Site of action; Streptococcus pneumoniae; Vaccines


Infection with Streptococcus pneumoniae remains a common cause of acute otitis media, community-acquired pneumonia, bacteremia, and meningitis. For many years, penicillin was the mainstay of treatment for pneumococcal infections and was responsible for dramatic decreases in mortality caused by this organism. However, penicillin-resistant S. pneumoniae (PRSP) has been steadily increasing in prevalence since it was first described in Australia more than 30 years ago. As recently as the 1980s, drug-resistant strains of S. pneumoniae were still relatively uncommon in the United States; now they have become troublesome in some parts of the country.

This article discusses the epidemiology, mechanisms of resistance, susceptibility testing, prevention, treatment, and clinical importance of PRSP infection.

Epidemiology

Penicillin resistance was first described in 1945 among mutant strains of pneumococci in vitro. Clinical isolates of S. pneumoniae with reduced susceptibility to penicillin were first reported in Boston in 1965. Penicillin minimum inhibitory concentrations (MICs) of 0.1 and 0.2 μg/mL were reported for 2 of the 200 isolates tested. Despite their findings, the investigators failed to recognize the clinical significance of their discovery. The first pneumococcal strain with reduced susceptibility to penicillin (MIC, 0.6 μg/mL) for which clinical relevance was recognized was reported in 1967 after being isolated from a 25-year-old Australian woman. During the next decade, several alarming reports were published documenting worldwide spread of pneumococci with reduced susceptibility to penicillin-resistant strains of S. pneumoniae. Penicillin has largely been abandoned in favor of cefotaxime or ceftriaxone. Vaccination remains an underutilized strategy in at-risk populations. The clinical importance of penicillin resistance among pneumococci is still uncertain.

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Therapy Update  Streptococcus pneumoniae

The Therapy Update section provides concise analytical reviews of narrowly defined, important topics in pharmacotherapy. Priority is given to articles that focus on new or emerging standards in drug therapy. Articles are not intended to be comprehensive reviews of drugs or disease states and their treatment.

In 1977, pneumococci exhibiting penicillin resistance (MIC, ≥2.0 µg/mL) were isolated, indicating a new era in pneumococcal resistance.14 By the early 1980s, worldwide distribution of multidrug-resistant pneumococci had been described.15

Because of the widespread isolation of pneumococci with various degrees of resistance, the Centers for Disease Control and Prevention (CDC) has suggested a standardized classification of resistance levels. CDC defines susceptibility of S. pneumoniae to penicillin as an MIC of ≤0.06 µg/mL. All isolates for which the MIC is ≥0.1 µg/mL are considered nonsusceptible. Isolates that are nonsusceptible are characterized further as intermediate (MIC, 0.1–1.0 µg/mL) or resistant (≥2.0 µg/mL). Isolates for which the MIC is ≥2.0 µg/mL were previously referred to as displaying high-level resistance; this terminology is no longer advocated by CDC.16

During the 1980s, the incidence and pattern of penicillin resistance among pneumococci remained fairly stable.17 Between 1979 and 1987, nonsusceptible pneumococci accounted for approximately 5% of the strains recovered in the United States. During the same period, resistant strains were rare—approximately 0.02% of isolates. By the early 1990s, however, a dramatic increase in the frequency of isolation of nonsusceptible pneumococci was reported.18,19 Barry et al.19 reported that 22% of pneumococcal isolates were intermediate-resistant or resistant to penicillin. Even more alarming than the increase in the frequency of reduced susceptibility has been an increase in the frequency of resistance. Penicillin-resistant organisms accounted for 2.6% of strains in 1991–92, versus 7.3% in 1992-93.18,19 Doern and colleagues,20 in a nationwide surveillance of S. pneumoniae susceptibility patterns in the United States in 1994 and 1995, reported reduced susceptibility to penicillin in 23.6% of isolates: intermediate resistance in 14.1%, and resistance in 9.5%. This study also highlighted the tremendous geographic variability in reported rates of resistance—from 2.1% to 52.9%—and noted that resistant pneumococci were isolated more frequently from children five years of age or younger than from all other age groups (12.6% versus 7.9%).

In 1997 the results of the TRUST (Tracking Resistance in the United States Today) study, a nationwide surveillance of adult respiratory-tract pathogens, were reported.21 Four hundred thirty-four centers in 45 states participated in this study during the respiratory infectious illness season of 1996–97. S. pneumoniae was the most common respiratory-tract pathogen encountered, with over 9000 isolates recovered. Thirty-three percent of the isolates had reduced susceptibility to penicillin (MIC, ≥0.1 µg/mL); of these, 13.6% were resistant (≥2.0 µg/mL). Cross-resistance to several other antimicrobials commonly used to treat community-acquired respiratory infections, such as erythromycin and trimethoprim–sulfamethoxazole, was also observed. Historically, penicillin-resistant pneumococci have been recovered more frequently from children five years of age or younger than from other age groups. Although young children are still at risk for resistant infections, an increased frequency of drug-resistant pneumococci has been encountered in adults.22 Risk factors for an infection secondary to a resistant pneumococcal strain include hospitalization, prior exposure to an antimicrobial agent, and tobacco use.22,23

Mechanisms of resistance

Pneumococcal resistance to β-lactam antibiotics occurs through structural alterations in the penicillin-binding proteins (PBPs) of the bacterial cell wall. These six high-molecular-weight enzymes produce peptidoglycan and are the usual binding sites for β-lactams. The pneumococcal genes encoding PBPs are termed mosaic genes because they may contain DNA sequences that are nonpneumococcal in origin.1 While both penicillin-susceptible S. pneumoniae (PSP) and PRSP contain mosaic genes, resistant isolates appear to contain more variability in their PBPs, which results in variations in susceptibility. The origin of these nonpneumococcal DNA pieces is not known, but they may have been acquired from other bacteria, such as viridans streptococci.1

Mosaic genes, decrease the affinity of PBPs for β-lactams and thus decrease these agents’ effectiveness. Since cephalosporins bind to different PBPs than penicillin, cephalosporins and penicillins may not be affected to the same extent. For example, ceftaxime and ceftriaxone may retain activity in the face of altered PBPs, while penicillin may not; the converse may also occur, although it is much less likely. Isolates displaying resistance to cephalosporins are not always resistant to penicillin, underscoring the importance of susceptibility testing. Infections by strains with intermediate resistance may be successfully treated with large dosages of β-lactams. Isolates that have a penicillin MIC of ≥1.0 µg/mL are more likely to be resistant to non-β-lactam antimicrobials, such as chloramphenicol, trimethoprim–sulfamethoxazole, erythromycin, tetracycline, and aminoglycosides, in addition to penicillin.1 Resistance to chloramphenicol, tetracycline, and erythromycin appears to be chromosomally mediated. Resistance to trimethoprim–sulfamethoxazole is attributed to trimethoprim and occurs by a decrease in the affinity of trimethoprim for its target enzyme, dihydrofolate reductase.24 It appears that pneumococci have incorporated or shared DNA with nonpneumococcal bacteria.

including gram-negative microbes, in order to acquire drug resistance. The genes that encode resistance to erythromycin, tetracycline, and aminoglycosides are termed ermB, tetM, and aphA3, respectively. The ermB gene is also found in some Escherichia coli and Klebsiella species, tetM is found in resistant Haemophilus and Neisseria species, and aphA3 is found in staphylococci, Enterococcus faecalis, and Helicobacter species.

Until the recent introduction of quinolone antimicrobials with an improved spectrum of activity against gram-positive organisms, quinolones did not possess sufficient activity to be clinically useful against S. pneumoniae. One of the genes responsible for resistance to quinolones is gyrA, which encodes the A subunit of DNA gyrase, the site of action of quinolone antimicrobials.26 Newer quinolones may be potent against S. pneumoniae despite mutations in the gyrA gene and may be useful for treating infections caused by this organism.27 Monitoring for resistance to quinolones among S. pneumoniae isolates will be important as the use of these drugs increases.

Like other bacteria, S. pneumoniae has a number of mechanisms that confer resistance to a variety of antimicrobials. The mechanism of resistance to β-lactams is not the production of β-lactamases, as is common in other bacteria, but alterations in PBPs resulting from mosaic genes. Chromosomally mediated resistance is the primary mechanism of resistance to non-β-lactam antimicrobials.

**Susceptibility testing in vitro**

All isolates of S. pneumoniae obtained from normally sterile sites should be tested to determine the MICs of penicillin and of cefotaxime or ceftriaxone for them. If the isolate is obtained from cerebrospinal fluid (CSF), vancomycin and rifampin MICs should also be determined.16,28 The method of MIC determination may differ with the laboratory, but all methods should conform to the standards of the National Committee for Clinical Laboratory Standards.16

Quantitative tests, such as the E-test and the broth microdilution technique, provide the most accurate information.29 The E-test is a simple commercial test consisting of a plastic strip containing a concentration gradient of an antimicrobial. The strip containing the antimicrobial is placed on an agar plate containing the test isolate, and after a period of incubation the MIC is determined by visualizing where the zone of inhibition intersects the test strip. This test is much easier than the broth microdilution technique, which requires preparation of a microtiter tray with serial dilutions of the antimicrobial being studied.

If neither of these tests is available, the oxacillin disk-diffusion method may be used. A small disk containing 1 µg of oxacillin is placed on agar containing the test organism. If the zone of inhibition around the disk is ≥20 mm, the isolate is considered susceptible; if the inhibition zone is ≤19 mm, the isolate is considered nonsusceptible.16 The major disadvantage of the oxacillin disk-diffusion method is that it can determine only whether an isolate is susceptible or nonsusceptible; to distinguish intermediate resistant from resistant isolates, further testing by the broth microdilution or E-test method is required. The oxacillin disk-diffusion test was designed to be sensitive in detecting nonsusceptible isolates, but the specificity of the test is lower than with microdilution tests. Some isolates identified as nonsusceptible by the oxacillin disk-diffusion method are found to be susceptible by quantitative MIC testing; the reverse is very uncommon. All culture and susceptibility tests may require up to 72 hours to yield complete results.

Because strains resistant to penicillin are more likely to be resistant to other antimicrobials as well, susceptibility to drugs such as trimethoprim-sulfamethoxazole and macrolides should often be determined simultaneously with susceptibility to penicillin by the broth microdilution or E-test method. Routine testing of S. pneumoniae for susceptibility to vancomycin is not currently warranted. Time permitting, susceptibility testing is a very important component of drug selection for the treatment of infections caused by S. pneumoniae.

**Evidence-based guidelines for treatment**

The inability to perform large, randomized, controlled clinical trials of agents for the treatment of infections caused by PRSP has led to differing opinions on how to treat these infections empirically. The best available data have been collected from case series and describe the drug used, the penicillin or cephalosporin MIC for the cultured organism, and the clinical outcome. Attempts to correlate clinical success (or failure) rates with the level of resistance exhibited by isolates have been made by some authors.30

**Otitis media**

Several reviewers have advocated amoxicillin as the drug of choice for the initial treatment of acute otitis media (AOM), even in regions with a high prevalence of PRSP.31-33 In a study of children ages two months to 15 years in rural Kentucky, amoxicillin 60–80 mg/kg/day was responsible for a 63% clinical success rate in patients from whom S. pneumoniae resistant to penicillin was isolated.34 Recommendations for alternative agents for resistant strains include amoxicillin-clavulanate potassium (with or without additional amoxicillin) and various cephalosporins, including injectable agents such as ceftriaxone.31,32,35 Amoxicillin has the pharmacodynamic advantage of increased time above the MIC for resistant isolates compared with oral cephalosporins.36 In the rural Kentucky study, amoxicillin-clavulanate potassium at a daily dose of amoxicillin 80 mg/kg and clavulanic acid 10 mg/kg had a 76% clinical success rate in children with resistant infections.34
A large, multicenter, open-label trial examined the efficacy of amoxicillin–clavulanate potassium, at a daily dose of amoxicillin 40 mg/kg and clavulanic acid 10 mg/kg, in the treatment of AOM in children ages three months to 12 years. The overall clinical success rate in the United States, evaluated at days 12–14, was 88% (70 of 80 children). Of the 80 children, only 17 were considered to have resistant strains; 14 (82%) of them were treated successfully. The success rate for patients with resistant isolates treated with amoxicillin–clavulanate potassium was not significantly different from the overall success rate.

Of the oral second-generation and third-generation cephalosporins, cefuroxime, cefprozil, and cepodoxime have the highest in vitro activity against penicillin-resistant pneumococci, and loracarbef, cefaclor, and cefixime have the least activity. Dagan et al. randomly assigned children ages 6–36 months with AOM caused by S. pneumoniae to receive cefaclor 40 mg/kg/day or cefuroxime axetil 30 mg/kg/day for 10 days. Both cephalosporins were clinically successful in treating children with susceptible strains, but cefuroxime tended to be more efficacious against resistant infections (bacteriologic success rate, 79% [15 of 19 isolates]) than cefaclor (42% [5 of 12]). The overall bacteriologic success rate for either agent against PSSP strains was 94%, but there was significantly less success against PRSP strains (65%).

Two other studies have demonstrated decreased success rates for cephalosporins against AOM due to PRSP. Barry et al. evaluated raw data from four clinical studies in a total of 219 children ages three months to 10 years with AOM treated with β-lactam antibiotics for 10 days. The clinical response rate in the PSSP group was 92% (152 of 166), which was significantly greater than the 81% response rate in the PRSP group (43 of 53). Gehanno et al. found that the clinical efficacy of cefuroxime axetil 30 mg/kg/day in children under the age of five years with AOM was correlated with the MIC for the isolate. The overall success rate was 86% (72 of 84). When stratified by penicillin MIC, success rates were 93% (39 of 42) for susceptible isolates (MIC, <0.1 µg/mL), 90% (9 of 10) for intermediate isolates (0.1–1 µg/mL), and 75% (24 of 32) for resistant strains (≥2 µg/mL), indicating a reasonable correlation between worsening clinical outcome and increasing level of resistance.

These studies should raise some concern among clinicians treating children with AOM empirically. Initial treatment with amoxicillin 40 mg/kg/day remains the first-line therapy for otitis media in children and adults. The dosage may be increased to 80 mg/kg/day if the response within two days is inadequate. In children who have a history of recurrent otitis media, who have not responded to amoxicillin, or who have a high likelihood of harboring a highly resistant organism, the following alternative agents may be used: amoxicillin–clavulanate potassium at a daily dose of amoxicillin 40 mg/kg and clavulanic acid 10 mg/kg, with or without additional amoxicillin at 40 mg/kg/day, or an oral second- or third-generation cephalosporin, such as ceftizoxime or cefprozil at 30 mg/kg/day. Although the combination of amoxicillin–clavulanate potassium does not offer increased activity against PRSP over amoxicillin alone, its increased activity against other common pathogens in otitis media (e.g., Haemophilus influenzae, Moraxella catarrhalis) makes it a rational alternative in patients refractory to amoxicillin monotherapy. Second-generation and third-generation oral cephalosporins are more active against gram-negative pathogens than amoxicillin but are probably not as effective against known PRSP isolates. For strains refractory to treatment with oral agents, an injectable second- or third-generation cephalosporin or vancomycin may be indicated.

Pneumonia

As with otitis media, there is some disagreement over the best initial agent to use in treating pneumococcal pneumonia. Some authors continue to emphasize the use of injectable penicillin as a first-line agent, stating that treatment failure is much less likely than in meningitis caused by a strain with the same level of drug resistance. Others recommend initial use of cefuroxime, cefotaxime, or ceftriaxone. Available results of clinical studies may be used to support either alternative; this emphasizes the need for controlled clinical trials designed to document outcomes in these patients.

A number of studies have been unable to document differences in outcomes or mortality rates between patients infected by PSSP and patients infected by PRSP. An observational study in 78 children with pneumococcal pneumonia who were treated conventionally did not find a difference in clinical outcomes between patients with PSSP and patients with PRSP. The author identified underlying disease as a significant risk factor for infection with a resistant organism. Underlying disease was also identified as a risk factor for mortality in an earlier case-control study of pneumococcal pneumonia. This relationship was also evident in a study of 504 adult patients by Pallela et al. The authors found a significant difference in mortality rates between patients with PRSP-associated pneumonia (35%) and patients with PSSP-associated pneumonia (24%). However, after correction for other predictors of mortality, there was no significant difference. This suggests that underlying disease is a more significant risk factor for mortality than the susceptibility of the infecting organism.

Currently recommended initial treatment of pneumococcal pneumonia in otherwise healthy patients requiring hospitalization consists of cefuroxime, ceftriaxone, or cefotaxime. Therapy should be altered on the basis of the clinical response and not solely the
MIC; if a patient is infected by a nonsusceptible strain but is responding to therapy, no change in antimicrobial therapy is warranted. In patients with underlying disease or other risk factors for pneumococcal infection, initial therapy with cefotaxime or ceftriaxone and vancomycin may be more conservative, as there is an increased risk of mortality overall in these patients. Therapy may be altered depending on the susceptibility of the organism and the patient’s response.

Meningitis

The consensus among recent reviews is that penicillin should no longer be used as initial treatment for pneumococcal meningitis. Several authors advocate monotherapy with a third-generation cephalosporin, either cefotaxime or ceftriaxone, while others suggest that initial therapy should include the combination of cefotaxime or ceftriaxone with vancomycin. The decision to change to alternative agents, including penicillin, is then made on the basis of culture and susceptibility test results.

Clinical studies have shown cefotaxime and ceftriaxone to be reasonable first-line agents for meningitis. Viladrich et al. investigated a series of 63 adult patients with 66 episodes of pneumococcal meningitis at a teaching hospital in Barcelona, Spain. Seventy-seven percent (51 of 66) of these episodes resulted from PSSP and the rest from PRSP. The overall mortality rates were not significantly different—33% and 20% for the patients with PSSP and PRSP, respectively. Of 13 patients yielding resistant isolates, 5 were treated with high-dose penicillin (300,000–500,000 units/kg/day) and 8 with cefotaxime (200–250 mg/kg/day). Three of the penicillin-treated patients were cured, one died, and the other was eventually treated with vancomycin and survived. All three of the patients successfully treated with penicillin produced isolates with penicillin MICs of 0.25–0.5 µg/mL, while the isolates from the other two were resistant (≥2 µg/mL). Of the eight cefotaxime-treated patients, seven survived. The authors concluded that, although penicillin is potentially effective even against nonsusceptible organisms, it should not be the first-line agent for pneumococcal meningitis. Instead, either cefotaxime or ceftriaxone should be initiated and may be changed to penicillin if the strain is found to be susceptible.

Tan et al. reported on a series of 10 children with meningitis due to a penicillin-resistant pneumococcus. Isolates from five children had a cefotaxime MIC of ≥0.5 µg/mL, and the other five children yielded isolates with an MIC of ≤0.25 µg/mL. All 10 patients received cefotaxime 200–225 mg/kg/day or ceftriaxone 50 mg/kg every 12 hours and had a successful outcome. Only 1 of the 10 had an adverse event (mild bilateral hearing loss). The authors suggested that either cefotaxime or ceftriaxone is indicated as initial therapy for pneumococcal meningitis in areas where high-level cephalosporin resistance (MIC, ≥2 µg/mL) is uncommon.

Chloramphenicol is no longer recommended for use in the treatment of pneumococcal meningitis. Friedland and Klugman investigated the utility of chloramphenicol for treating PRSP in a series of 68 children with pneumococcal meningitis. Twenty-five patients had chloramphenicol-susceptible PRSP for which chloramphenicol 75–100 mg/kg/day was started as initial therapy; however, 20 (80%) of these patients had an unsuccessful outcome, defined as death, serious neurologic deficit, or poor clinical outcome. Of the 43 patients with PSSP, 14 (33%) had unsuccessful outcomes when treated with penicillin G 400,000 units/kg/day. Therefore, chloramphenicol is not recommended for use in the treatment of meningitis caused by nonsusceptible S. pneumoniae.

The current literature supports ceftriaxone or cefotaxime plus vancomycin as initial therapy for pneumococcal meningitis. If the MIC of antimicrobial for the isolate is ≤0.1 µg/mL, then therapy can be changed to penicillin alone, which will most often be less expensive and carry less risk of promoting microbial resistance to third-generation cephalosporins and vancomycin. Alternatively, the cephalosporin may be continued alone. For intermediate resistant isolates (MIC, 0.1–1.0 µg/mL), the third-generation cephalosporin should be continued alone; vancomycin may be discontinued. When the MIC is ≥2.0 µg/mL or there is no clinical improvement, the combination of the cephalosporin and vancomycin should be continued. Vancomycin should not be used alone in the treatment of S. pneumoniae-associated meningitis.

The role of vaccination

Currently available pneumococcal vaccines are composed of purified capsular polysaccharide antigens from 23 serotypes of S. pneumoniae, representing 85–90% of the serotypes responsible for invasive infections in children and adults in the United States. Of the seven serotypes most commonly associated with drug resistance, six are represented in the vaccine. Although serotype 6A is not found in the vaccine, some protection against it may be provided because of serologic cross-reactivity with type 6B.

The most recent guidelines from the Advisory Committee on Immunization Practices (ACIP) recommend vaccination of several patient populations. All persons 65 years of age or older who either have unknown vaccination status or were under the age of 65 when last vaccinated and are now five or more years older should receive pneumococcal vaccination. Other persons at risk for pneumococcal infection, such as those with chronic illnesses, patients who are immunocompromised, and those in special social settings (e.g., skilled-nursing facilities) should receive vaccination against S. pneumoniae before the age of 65. Vaccination is not recommended for children under the age of two years because they do not reliably develop an immune re-
response to the polysaccharide vaccine. Even though studies indicate that children attending daycare centers are at increased risk for infection with S. pneumoniae strains with reduced susceptibility to penicillin, routine immunization of this group is not yet recommended by ACIP, unless other risk factors for infection are present.

Routine revaccination of immunocompetent persons previously vaccinated is not recommended. A second dose may be administered three to five years after the primary immunization in high-risk populations and is recommended for persons 65 years of age or older who were vaccinated more than five years previously and were less than 65 years old at the time of the original vaccination. The benefit and safety of receiving three or more doses of vaccine are unclear, and this practice is not currently recommended.

Although the polysaccharide pneumococcal vaccine is recommended for several populations considered to be at high risk, studies have consistently failed to show vaccine efficacy in these populations. Case-control studies able to demonstrate efficacy have yielded estimates ranging from 36% to 67%. In each case, the overall efficacy rates were achieved solely in low-risk populations. Similar results were obtained by Fine et al. in a meta-analysis of published studies of vaccine use. In fact, none of the studies evaluated demonstrated efficacy in high-risk populations.

Although these results certainly do call into question the clinical efficacy and cost-effectiveness of the polysaccharide vaccine in several populations for which ACIP currently advocates immunization, they also strengthen the argument for immunization in the most frequently targeted population—persons 65 years of age or older who lack other risk factors. Three studies looking specifically at the immunocompetent elderly produced a consistent 70–75% estimate of efficacy. This is an important finding in light of the underutilization of pneumococcal vaccine in this population.

Underutilization of the polysaccharide vaccine, especially in the elderly, has been well documented. A national health objective for the year 2000 is vaccination rates of ≥60% among persons at high risk, including those 65 or older. Although the cumulative rate of pneumococcal vaccination has been on the rise since the polysaccharide vaccine was released for marketing in 1983, the current estimate of vaccine use among persons ≥65 years of age is only 28%.

Children under the age of two years are especially susceptible to invasive pneumococcal infections and are at an increased risk for drug-resistant infections. Commercially available polysaccharide vaccines are not able to elicit an adequate immune response in young children. This has led to the development of pneumococcal capsular polysaccharide-protein conjugate vaccines that employ the same principle used in H. influenzae type b vaccines—coupling the polysaccharide to a carrier protein, which increases immunogenicity. Preliminary antibody titer test results show that these conjugate vaccines, containing a range of serotypes, are safe and consistently elicit an immunologic response in infants as young as two months. Researchers have not determined threshold antibody levels required to provide adequate protection clinically, so laboratory-based comparisons of vaccine formulations are arbitrary at this point. It remains to be determined whether the conjugate vaccine will surpass the polysaccharide vaccine and actually be able to prevent disease in young children and adults at high risk of infection; multicenter trials are under way.

Clinical importance of penicillin resistance

The clinical importance of penicillin resistance among pneumococci is still uncertain. Several reports seem to suggest that patient outcomes are similar between individuals with PRSP and those with PSSP, even when initial therapy consists of a β-lactam. High dosages of β-lactams should produce drug concentrations at the site of infection adequate to kill strains with intermediate susceptibility to penicillin. Although patient outcomes may not be affected, financial costs may be influenced by the fact that larger dosages are required. The clinical impact of reduced drug susceptibility has been less well established for isolates exhibiting penicillin resistance. Since many of these isolates are cross-resistant to other non-β-lactam antimicrobials, the agents available for use are limited. Generally, this means that more expensive intravenous therapies and close patient monitoring may be required. The illness of greatest concern is pneumococcal meningitis. In this clinical situation, CSF drug concentrations are already low, and reduced susceptibility of the infecting pathogen may further compromise drug efficacy. Reduced susceptibility can affect the decision to use corticosteroid therapy in pediatric patients, as there may be concern that the reduction in inflammation will hinder CSF penetration by the antimicrobial.

Weis et al. recently reported that infection with a nonsusceptible isolate of S. pneumoniae was associated with increased hospital costs. Patient costs were analyzed over a five-year period for all individuals treated as inpatients for a pneumococcal infection. Patients were grouped by whether their infection was hospital or community acquired and by the susceptibility of the infecting strain. Patients with a hospital-acquired, nonsusceptible isolate cost the institution approximately $16,000 more to treat than patients with penicillin-susceptible bacteria (p < 0.05). The difference in treatment costs was linked to increased patient care requirements (e.g., critical care beds, nursing services). It appears that, even if drug costs and clinical outcomes do not differ between patients infected with susceptible and nonsusceptible pneumococci, infection with a resistant organism does increase the overall cost of therapy, at least for hospitalized patients.
Conclusion

Changing patterns in the susceptibility of *S. pneumoniae* make selecting appropriate therapy increasingly difficult. Key considerations include the site of infection and the level of susceptibility. Upper-respiratory-tract infections with *S. pneumoniae* strains displaying intermediate susceptibility to penicillin may respond to β-lactams because antimicrobial levels at the infection site may adequately exceed the MIC. Life-threatening infections, including meningitis, should be treated with cefotaxime or ceftriaxone; the addition of vancomycin may be necessary if the MIC is ≥2.0 µg/mL.

References

Therapy Update

Streptococcus pneumoniae


