

ASHP Therapeutic Position Statement on Strategies for Identifying and Preventing Pneumococcal Resistance

Statement of Position

The American Society of Health-System Pharmacists (ASHP) supports the establishment of state and national surveillance systems to track the prevalence of drug-resistant *Streptococcus pneumoniae* so that appropriate antimicrobial regimens can be used to treat infections caused by this common community-acquired pathogen.

ASHP supports continued educational efforts to promote the rational use of antimicrobials as a strategy for preventing the development of drug-resistant bacteria.

ASHP supports the vaccination of all persons at risk for acquiring pneumococcal disease. Use of pneumococcal vaccines is a reliable strategy to decrease the morbidity and mortality associated with invasive infections due to *S. pneumoniae*.

Background

S. pneumoniae, also known as pneumococcus, is the most common cause of community-acquired bacterial respiratory-tract infections. It is a frequent cause of meningitis, bacteremia, otitis media, and community-acquired pneumonia. Infections caused by *S. pneumoniae* have been associated with increased morbidity and mortality, especially in children under two years of age and elderly adults. Infections caused by *S. pneumoniae* have typically been successfully treated with a variety of antimicrobials, including penicillin, cephalosporins, and erythromycin. In the early 1990s the first reports of penicillin nonsusceptible *S. pneumoniae* (PNSP) began to appear in the United States; penicillin nonsusceptible strains include both intermediately resistant and resistant strains of *S. pneumoniae*. During the past decade the reports of increasing resistance of *S. pneumoniae* to penicillin and cephalosporins continued, and in the late 1990s reports of increasing resistance to trimethoprim-sulfamethoxazole, macrolides, and fluoroquinolones began to appear. Many isolates developed resistance to multiple classes of drugs and became known as multi-drug resistant *S. pneumoniae* (MDRSP). The increasing prevalence of MDRSP is creating a challenge for health care providers in treating this common community-acquired pathogen.

The clinical significance of drug-resistant *S. pneumoniae* on treatment outcomes is unclear. Most of the available data on clinical outcomes are from retrospective reviews, case-control studies, and case reports. There is evidence that meningitis due to PNSP does not respond to treatment with either penicillin or standard doses of cephalosporins, leading to poor clinical outcomes.¹ In contrast, there does not appear to be a significant difference in clinical outcome, primarily mortality, when pneumonia or other nonmeningeal infections due to PNSP are treated with penicillin or cephalosporins. On the contrary, macrolides and fluoroquinolones with poor in vitro activity against *S. pneumoniae* have been associated with poor clinical outcomes and even treatment failures. It is likely that clinical outcomes be depend on the mechanism and degree of resistance, the site of infection, and the pharmacokinetic and pharmacodynamic characteristics of the antimicrobial agents used in treatment.

Definitions. NCCLS, previously known as the National Committee for Clinical Laboratory Standards, revised the definitions of *S. pneumoniae* susceptibility to several antimicrobials in its 2002 standards. *S. pneumoniae* resistant to penicillin is defined in terms of the minimum inhibitory concentration (MIC) of penicillin. Strains may be distinguished as susceptible (MIC < 0.06 µg/mL), intermediately resistant (MIC 0.12–1.0 µg/mL), or highly resistant (MIC ≥ 2 µg/mL).² The most notable change in 2002 was the increase in breakpoint values for susceptibility of nonmeningitis isolates of *S. pneumoniae*. NCCLS took into account the pharmacokinetic and pharmacodynamic factors of a drug in redefining susceptibility breakpoints. The definition of multidrug-resistant *S. pneumoniae* is a strain resistant to three or more classes of antimicrobials.

Epidemiology. Numerous national and international surveillance studies have been conducted to determine the prevalence of *S. pneumoniae* resistance.^{3–7} These networks used similar methodologies and specimens: clinical isolates of *S. pneumoniae* from sterile body sites or the respiratory tract, with susceptibility testing in accordance with NCCLS standards. Although these studies showed differing resistance rates to the antimicrobials tested, some common

Table 1.

Susceptibility of *Streptococcus pneumoniae* Isolates to Commonly Used Antimicrobials

Ref.	n	% Resistant Isolates					
		IR Penicillin	Resistant Penicillin	Ceftriaxone ^a	Erythromycin	Trimethoprim-Sulfamethoxazole	Levofloxacin
3	3,447	9.6	15.5	NA ^b	19.2	24.0	0.7
4 ^c	2,432	12.0	25.0	4.3	28.8	37.5	NA
5	10,012	14.2	21.2	NA	27.9	NA	1.0
6	1,531	12.7	21.5	NA	25.7	30.3	0.3
7	7,671	15.5	18.4	1.7	NA	26.0	0.9

^aNCCLS nonmeningitis breakpoints.

^bNA = not applicable.

^cU.S. data only.

trends emerged (Table 1). The incidence of strains highly resistant to penicillin has surpassed that of intermediately resistant strains. The rates of resistance to non- β -lactams have also increased: the prevalence of macrolide resistance is 20–30%, and trimethoprim–sulfamethoxazole resistance ranges between 24% and 38%. *S. pneumoniae* resistance to levofloxacin is hovering around 1%. However, there have been reports from Canada⁸ and the Centers for Disease Control and Prevention (CDC)⁹ of increasing resistance of *S. pneumoniae* to fluoroquinolones. Most fluoroquinolone-resistant isolates are resistant to other antimicrobials. Fluoroquinolone-resistant organisms are more likely to be found in persons over 65 years of age, the population with the highest use of fluoroquinolones.

Persons at Risk. The greatest risk factor for becoming infected with a drug-resistant strain of *S. pneumoniae* is prior antimicrobial use. Other risk factors include carriage of *S. pneumoniae*, daycare attendance, exposure to children who attend daycare, severe medical comorbidities, immunosuppression, and high alcohol intake.¹ Smoking has been identified as a risk factor for developing invasive *S. pneumoniae* infections.¹⁰ The risk of invasive *S. pneumoniae* infections is 4-fold if the patient is a smoker and 2.5-fold if the patient is exposed to secondhand smoke. The risk of invasive disease declines over time for persons who have stopped smoking.

Mechanisms of Resistance. Resistance of *S. pneumoniae* to β -lactams is due to genetic mutations leading to alterations in three or four of the five high-molecular-weight penicillin-binding proteins (PBPs).¹¹ The degree of *S. pneumoniae* resistance is dependent on which PBPs are involved and the affinity of the β -lactam agent to the PBP. The differences in expression of these PBPs explain the differences in susceptibility to a variety of β -lactams.

S. pneumoniae resistance to macrolides occurs primarily through two mechanisms: active drug efflux (M phenotype) or ribosomal modification (MLS_B phenotype).¹² Active drug efflux confers resistance to all agents within the class, whereas ribosomal modification confers resistance not only to the macrolides but also to clindamycin and streptogramins. Approximately 75% of macrolide-resistant *S. pneumoniae* found in the United States is attributable to active drug efflux.

Resistance of *S. pneumoniae* to fluoroquinolones is primarily a result of mutations of the *parC* and *gyrA* genes, although efflux pumps may also play a role.¹³ Alterations in the *parC* subunit of topoisomerase IV result in the reduced susceptibility of *S. pneumoniae* to gatifloxacin, levofloxacin, and moxifloxacin. This single-step mutation is difficult to detect clinically because isolates with a *parC* mutation are reported as susceptible using standard laboratory testing. This is concerning because isolates with single-step mutations are the progenitors for fully drug-resistant strains of *S. pneumoniae*, which have additional mutations in the *gyrA* subunit of DNA gyrase.

Establishment of Surveillance Systems

Surveillance systems are an integral component of combating bacterial resistance. The data gathered from surveillance systems can be used for many purposes, such as identifying and tracking global outbreaks, setting public health policy, determining appropriate treatments for different infections, and heightening awareness of health care providers to local resistance trends that may affect the routine care of patients.

Health systems should develop a mechanism for the surveillance of bacterial resistance. Ideally, the surveillance system should identify trends in bacterial susceptibility patterns and correlate this with antimicrobial use in both health systems and communities.¹⁴ The clinical microbiology laboratory, pharmacy, information systems, and infection control departments play important roles in maintaining an active surveillance system. Surveillance systems for tracking the prevalence of *S. pneumoniae* include two approaches, each providing differing types of information. The more common system uses culture data from clinical isolates causing invasive disease, which give an indication of the resistance patterns of strains actually causing clinical infection. The other approach determines the community *S. pneumoniae* carriage rate by testing nasopharyngeal swabs from individuals without clinical illness, demonstrating which strains could cause clinical infection. However, one study found that nasopharyngeal swabs overestimate the rate of *S. pneumoniae* colonization because of misidentification of oral streptococci as *S. pneumoniae*.¹⁵ The importance of accurately identifying *S. pneumoniae* and determining susceptibility cannot be overstated.

Guidelines for the treatment of common community-acquired infections developed by various national organizations can be found in the appendix. These guidelines incorporate data from large surveillance studies of microbial resistance to make recommendations for initial treatment regimens. Local surveillance data can be used to tailor national guidelines when developing local recommendations for empirical treatments.

Participation in an active surveillance system should not be limited to individual institutions. Health systems should actively participate in state and national surveillance initiatives. Sentinel surveillance, which incorporates data from a small number of laboratories to determine trends for a much larger area, can accurately detect large changes in the susceptibility of *S. pneumoniae*, but it infrequently detects emerging resistance profiles, such as the fluoroquinolone resistance of *S. pneumoniae*.¹⁶ Sentinel surveillance is also useful in showing trends in susceptibility over time. CDC, the Food and Drug Administration, and the National Institutes of Health have launched an action plan to combat antimicrobial resistance.¹⁷ One of the four major components of this plan is the enhancement of surveillance systems. CDC will coordinate efforts with state and local health departments to develop national, regional, state, and local surveillance networks. The data gained from this initiative can be used to target areas with a high prevalence of PNSP for pneumococcal vaccination programs and efforts to promote the judicious use of antimicrobials.

Rational Use of Antimicrobials

There is an abundance of literature showing the relationship between antimicrobial-use patterns and the development of resistance. However, the bulk of this literature has been generated from hospital or institutional studies and has little bearing on PNSP. Since *S. pneumoniae* is primarily a community-acquired pathogen, antimicrobial use in the outpatient setting has the greatest influence on the susceptibility profile of *S. pneumoniae*. Few studies have shown a relationship between outpatient prescription use and *S. pneumoniae* susceptibility patterns. In the United States, Diekema and colleagues¹⁸ found a positive correlation between high usage rates of outpatient

β -lactam agents and the decreased penicillin susceptibility of *S. pneumoniae*. No correlation was found between the use of other antimicrobial classes (e.g., macrolides, tetracyclines, and fluoroquinolones) and the decreased penicillin susceptibility of *S. pneumoniae*. Bronzwaer et al.¹⁹ found a relationship between high outpatient use of β -lactam agents and macrolides and the decreased penicillin susceptibility of *S. pneumoniae* in Europe. A major limitation of both of these studies was the failure to track patient adherence to prescribed regimens; however, these studies demonstrated that the community burden of high antimicrobial use is substantial and plays a role in the development of microbial resistance.

Several national organizations,¹⁴ CDC, and the World Health Organization have advocated judicious antimicrobial-use stewardship as a mechanism to limit the development of bacterial resistance. One of the cornerstones of antimicrobial-use stewardship is the appropriate use of antimicrobials. Approximately 50% of adults,²⁰ and over 20% of children's²¹ prescriptions for antibacterials are unnecessary. These agents were usually prescribed for treatment of the common cold, upper-respiratory-tract infections, and bronchitis, ailments often caused by viruses that do not respond to antibacterials.

Hennessy et al.²² attempted to demonstrate that decreased outpatient antimicrobial use could reduce the carriage of PNSP. In a controlled intervention trial in rural Alaska, investigators provided extensive education to the health care providers and the public on the management of respiratory-tract infections and the appropriate use of antimicrobials. They tracked the nasal carriage of penicillin-susceptible *S. pneumoniae* and PNSP, as well as antimicrobial use in the region for a three-year period. During the first year they found a significant decrease in the nasal carriage of PNSP and antimicrobial use. However, the carriage of PNSP increased to almost preintervention levels in the following two years of the study, despite the continued low rate of antimicrobial use. This suggests that changing antimicrobial-use patterns is only one part of solving a complex problem. Such changes will likely need to be coupled with other programs, including aggressive vaccination, to show a significant effect on decreasing the carriage of *S. pneumoniae*.

Education of health care providers and the public is essential for ensuring the rational use of antimicrobials. Pharmacists can play a significant role in educating both groups,²³ assuming roles as educators to assist in disseminating vital information that encourages the rational use of antimicrobials.

Educating the public about antimicrobial use and misuse is essential because consumers play a key role in drug utilization. In focus groups, patients have indicated that if physicians explain why an antimicrobial was not needed, they would be satisfied with not receiving a prescription for one.²⁴ For many reasons, most health care providers cannot or do not spend the time necessary to adequately educate their patients or patients' caregivers on the potential dangers of the inappropriate use of antimicrobials. Pharmacists are encouraged to assume responsibility for educating patients about these dangers. A mass media campaign geared to the public on the dangers of emerging infectious diseases has been underway for several years.²⁵ This campaign should be tailored for the needs of individual communities.

Vaccination

Infections caused by *S. pneumoniae* continue to cause significant morbidity and mortality despite the availability

of effective vaccines. Both the 23-valent pneumococcal polysaccharide vaccine (PPV) and the 7-valent pneumococcal conjugate vaccine (PCV7) have been shown to be highly effective in providing protection against the most commonly isolated pneumococcal serotypes that cause human disease, including those serotypes known to be antimicrobial resistant. While the use of these vaccines will not prevent the development of drug-resistant *S. pneumoniae*, they will likely prevent invasive infection caused by a drug-resistant organism. PPV is recommended for all adults aged 65 years or older.²⁶ It may also be given to select groups of high-risk patients over 2 years of age. This vaccine does not produce an adequate immunological response in children under 2 years old and should not be used in that population. PCV7 was added to the standard recommended pediatric vaccines in October 2000.²⁷ The PCV7 series should be given to all children beginning at age 2 months. The CDC National Immunization Program has established current recommendations for pneumococcal vaccine administration.²⁸

PPV was licensed in the early 1980s and has demonstrated good immunogenicity in both young and older adults; however, an individual will not develop an immune response to all 23 pneumococcal serotypes.²⁹ The reason for this is unclear. Despite the vaccine's long-standing availability and documented effectiveness, less than 60% of eligible persons actually receive it.³⁰ One of the Healthy People 2010 goals is for 90% of eligible adults to receive pneumococcal vaccine.³⁰ This is an excellent opportunity for pharmacists to improve the vaccination rate of older adult patients and help promote national health care goals.

Revaccination with PPV is recommended for adults over age 65 years if the first dose was administered when he or she was under 65 years old at the time of vaccination and at least five years have elapsed since the first dose.²⁶ In addition, persons younger than 65 years with immunocompromising conditions may receive a one-time revaccination if five years have elapsed since the first dose of PPV. Revaccination with PPV results in a somewhat blunted immune response and is associated with increased injection-site reactions.²⁹

PCV7 for children has been available since February 2000. Use of this vaccine has been shown to decrease the carriage rate of *S. pneumoniae* and the incidence of invasive pneumococcal disease, acute otitis media, and pneumonia in vaccinated populations.^{31,32} The rate of vaccine-specific serotype *S. pneumoniae* carriage in vaccinated children remains below the rate for nonvaccinated children over prolonged periods of time. Widespread vaccination of children with PCV7 has shown a "herd effect" in decreasing the carriage rate of *S. pneumoniae* in children, who are an important vector for the transmission of *S. pneumoniae* to other children and adults.³¹ This indirect effect was recently documented by the CDC Active Bacterial Core Surveillance Network, which found a decrease of 32% in invasive disease in adults age 20–39 years, 8% for those 40–64 years of age, and 18% for those 65 years or older.³² This is similar to what was seen with widespread use of the *Haemophilus influenzae* type B vaccine and the marked decrease in *H. influenzae*-related infections.

Most people who succumb to preventable infections had visited a health care provider in the preceding year but were not vaccinated.^{33–37} Clinicians need to ensure that people receive proper immunizations^{38,39} and pharmacists can promote vaccination efforts by serving as educators, facilitators, and vaccinators. Although vaccinations are typi-

cally administered in the ambulatory care setting, clinicians seize opportunities to vaccinate hospitalized patients as well. Pharmacists have demonstrated that they can increase the number of persons receiving needed vaccines in both inpatient and ambulatory care settings.⁴⁰

Summary

The incidence of drug-resistant *S. pneumoniae* continues to increase, causing significant morbidity and mortality. Health care providers should seize the opportunity to promote the judicious use of antimicrobials and aggressive vaccination with the pneumococcal vaccines as a means to lessen this significant health problem.

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Approved by the ASHP Board of Directors on April 15, 2004. Developed through the ASHP Commission on Therapeutics.

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The bibliographic citation for this document is as follows: American Society of Health-System Pharmacists. ASHP therapeutic position statement on strategies for identifying and preventing pneumococcal resistance. *Am J Health-Syst Pharm.* 2004; 61:2430–5.

Appendix—Selected Guidelines for the Treatment of Common Community-Acquired Respiratory-Tract Infections

Bronchitis

Snow V, Mottur-Pilson C, Hickner JM et al. for the American College of Physicians–American Society of Internal