Resistance among *Streptococcus pneumoniae:* Implications for Drug Selection

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***Streptococcus pneumoniae* is an important pathogen in many community-acquired respiratory infections in the United States and a leading cause of morbidity and mortality worldwide. Unfortunately, *S. pneumoniae* is becoming increasingly resistant to a variety of antibiotics. Results of recent surveillance studies in the United States show that the prevalence of penicillin-nonsusceptible *S. pneumoniae* ranges from 25% to >50%, and rates of macrolide resistance among pneumococci are reported to be as high as 31%. A high prevalence of resistance to other antimicrobial classes is found among penicillin-resistant strains. Newer quinolones (e.g., gatifloxacin, gemifloxacin, and moxifloxacin) that have better antipneumococcal activity in vitro are the most active agents and therefore are attractive options for treatment of adults with community-acquired respiratory infections. Efforts should be made to prevent pneumococcal infections in high-risk patients through vaccination.**

Streptococcus pneumoniae is an important pathogen in many community-acquired respiratory infections, including acute bacterial sinusitis, acute otitis media, community-acquired pneumonia, and acute exacerbations of chronic bronchitis, as well as in more invasive infections, such as meningitis and bacteremia. Since 1967, when a pneumococcal isolate resistant to both penicillin (MIC, 0.6 μg/mL) and tetracycline (MIC, 5 μg/mL) was isolated from a patient in Australia [1], resistant pneumococci have been identified globally in steadily increasing numbers, especially since the late 1980s (figure 1) [2, 4]. Rates of penicillin resistance among the pneumococci are as high as 60% in some parts of Latin America (table 1) and as high as 80% in some countries in Asia [5, 6].

EPIDEMIOLOGY OF DRUG-RESISTANT *S. PNEUMONIAE*

The worldwide spread of resistant pneumococci is thought to be related to the spread of a few highly resistant clones, such as serotypes 6B, 19F, and 23F [7, 8]. Population-based active surveillance surveys capture data from as many laboratories as possible within a given community; however, these findings may be more representative of the communities studied than of the world.

***Penicillin resistance among* S. pneumoniae.** The current National Committee for Clinical Laboratory Standards (NCCLS) [9] interpretive MIC breakpoints for penicillin are ≤0.06 μg/mL (susceptible), 0.12–1.0 μg/mL (intermediate), and ≥2.0 μg/mL (resistant). Isolates classified as either intermediately resistant or resistant are considered to be nonsusceptible. Breakpoints for amoxicillin, with or without clavulanate, are ≤2.0 μg/mL (susceptible), 4.0 μg/mL (intermediate), and ≥8.0 μg/mL (resistant).

Breakpoints for individual oral cephalosporins are not identical, and some cephalosporins (e.g., cefixime) do not have specific NCCLS breakpoints. For cefdinir and cefpodoxime, the breakpoints are ≤0.5 μg/mL
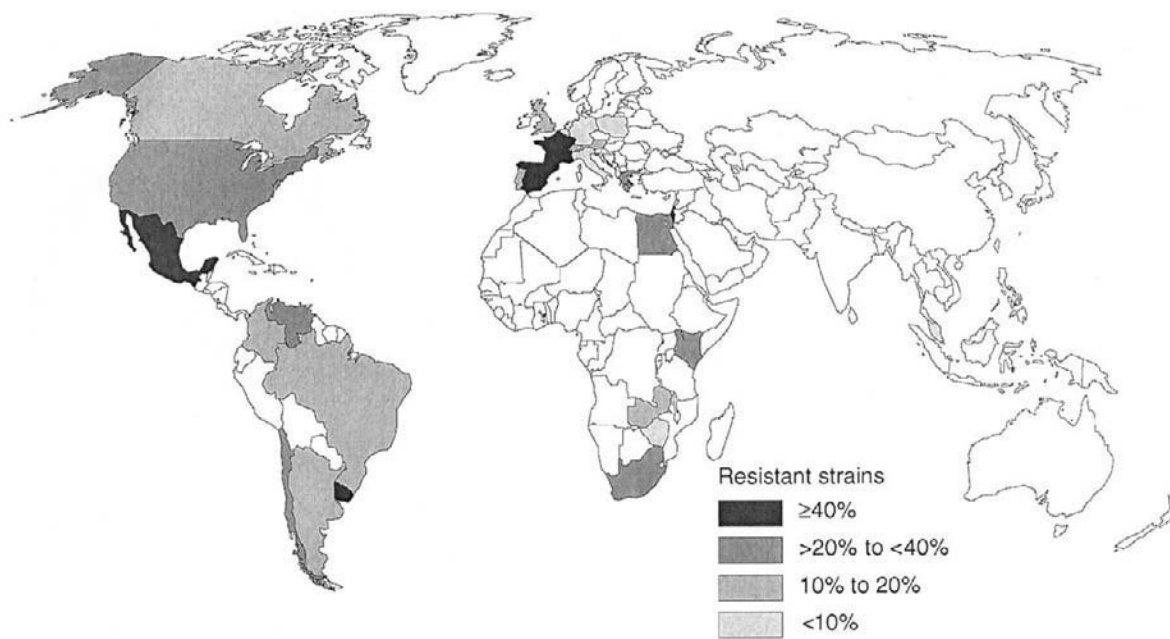
Figure 1. Worldwide prevalence and distribution of penicillin-resistant *Streptococcus pneumoniae* (1964–1998). Unshaded areas are those in which the prevalence is unknown (data from [2, 3]).

(susceptible), 1.0 μg/mL (intermediate), and ⩾2.0 μg/mL (resistant). For cefaclor and cefuroxime axetil, the breakpoints are higher: <1.0 μg/mL (susceptible), 2.0 μg/mL (intermediate), and ⩾4.0 μg/mL (resistant). The breakpoints for cefprozil and loracarbef are 2.0 μg/mL (susceptible), 4.0 μg/mL (intermediate), and ⩾8.0 μg/mL (resistant).

After the report of a resistant pneumococcal isolate in Australia [1], reports of penicillin-resistant pneumococci were sporadic until the late 1970s, when numerous isolates resistant to penicillin (MICs, 1–4 μg/mL) were identified in South Africa [2, 10]. Many of these strains were resistant to β-lactams, macrolides, tetracycline, chloramphenicol, and clindamycin [11]. In the late 1980s, the prevalence of penicillin-nonsusceptible *S. pneumoniae* in the United States was 4.0% [12], but, in less than a single decade, it increased to ~25% [13, 14]. Of interest was the increase in intermediate-level penicillin resistance, from 3.8% during 1987–1988 [12] to 18% in 1994 [14]. Results of recent surveillance studies in the United States show that the prevalence of penicillin-nonsusceptible *S. pneumoniae* ranges from 25% to >50%, and intermediate-level resistance ranges from 11% to 28% (table 2) [15–19]. In some parts of the world, rates of resistance are even higher (table 1).

Resistance of* S. pneumoniae *to other antimicrobials. As the use of nonpenicillin antimicrobials has increased, so has the development of resistance to these agents among pneumococci. However, rates of pneumococcal resistance to the quinolones are relatively low (typically <0.5%) [16, 18, 19]. Recent data from the Canadian Bacterial Surveillance Network show that the prevalence of pneumococcal isolates with cip-

rofloxacin MICs of ⩾4 μg/mL may be on the rise (the rate was 0% in 1993 and 1.7% in 1997), coincident with increased use of ciprofloxacin to treat adults in Canada [20]. In addition, increasing resistance to quinolones has been documented in Hong Kong and in Barcelona, Spain [21, 22]. Older quinolones (e.g., ciprofloxacin and ofloxacin) that have MICs of ~1.0–4.0 μg/mL are considered to have poor in vitro activity against pneumococci. Levofloxacin (the L-isomer of ofloxacin) has better activity, and the newer quinolones (e.g., gatifloxacin, gemifloxacin, and moxifloxacin) have much better in vitro activity, with lower MICs and better pharmacodynamics for activity against *S. pneumoniae;* they can be effective in treatment of community-acquired pneumococcal respiratory tract infections, such as acute bacterial sinusitis, acute exacerbations of chronic bronchitis, and pneumonia [23–25].

Resistance of *S. pneumoniae* to the macrolides and azalides (e.g., clarithromycin, erythromycin, and azithromycin) has been increasing since the late 1980s. In the United States, 0.2% of *S. pneumoniae* were resistant to macrolides in 1988 [12]. This increased to 6.4% in 1992, 10.6% in 1995, 13.9% in 1996, and 20.4% in 1999 [26, 27]. In recent US surveillance studies, rates of macrolide resistance among the pneumococci have been reported to be as high as 31% (table 3) [14, 16, 18, 28]. There also have been recent reports of clinical failure of macrolide treatment for infections caused by *S. pneumoniae* [29, 30].

Penicillin-resistant pneumococci also are resistant to trimethoprim-sulfamethoxazole (20%–35.9%) and tetracycline (8%–16.6%) [14, 17]. Resistance to vancomycin, both in vitro and in vivo, has been described in pneumococcal strains. How-

Table 1. Worldwide prevalence and distribution of penicillin-nonsusceptible *Streptococcus pneumoniae* in 1997–1998.

Geographic area	Prevalence of nonsusceptibility,[a] % of isolates
North America	
Canada	20.0
United States	34.7
Latin America	
Brazil	15.6
Colombia	16.5
Argentina	17.2
Venezuela	33.0
Chile	39.1
Mexico	60.0
Uruguay	60.0
Europe	
The Netherlands	3.2
Germany	7.2
Belgium	8.0
Italy	9.0
Austria	12.4
Switzerland	14.5
Portugal	17.1
United Kingdom	19.5
Greece	31.6
Spain	41.8
France	53.3
Israel	47.9

NOTE. Data are from the SENTRY Antimicrobial Surveillance Program and the Alexander Project (adapted from [5], with permission; additional data from [3]).

[a] Either intermediate-level (MIC, 0.12–1 μg/mL) or high-level (MIC, ≥2.0 μg/mL) resistance.

ever, it is doubtful that these findings are clinically relevant (table 3) [31–33]. Most strains of *S. pneumoniae* still are highly susceptible to rifampin, although this drug is not commonly used in the United States to treat pneumococcal infections.

Multidrug resistance. Pneumococci resistant to ≥3 separate classes of antibiotics are considered to be multiply resistant. The reasons that pneumococci develop simultaneous resistance to several antimicrobial classes are not clear, but some resistance determinants are carried together on the same transposon.

Multiply resistant pneumococci that are resistant to penicillin, tetracycline, erythromycin, clindamycin, trimethoprim-sulfamethoxazole, and chloramphenicol were first described in South Africa [34]. Today, isolation of multiply resistant pneumococci from both adults and children has been reported from around the world [2, 4, 14, 20, 31, 32]. Resistance to non–

β-lactam drugs tends to be more common among penicillin-nonsusceptible *S. pneumoniae* than among penicillin-susceptible pneumococci (table 4) [4, 14].

MECHANISMS OF ANTIMICROBIAL RESISTANCE AMONG *S. PNEUMONIAE*

Penicillins and other β-lactams. β-Lactam antimicrobials inhibit cell-wall synthesis by binding to penicillin-binding proteins (PBPs), which are responsible for maintenance of the cell wall. Resistance among *S. pneumoniae* to penicillins and β-lactams occurs after several sequential (stepwise), chromosomally mediated mutations to 3 or 4 of the 5 high–molecular-weight PBPs (1A, 1B, 2B, 2X, and 3); the pneumococci do not produce β-lactamase. Pneumococci likely obtained the β-lactam–resistance genes from viridans streptococci, such as *Streptococcus mitis* and *Streptococcus oralis;* the determinants then spread by means of transposons from pneumococcus to pneumococcus [35, 36]. Alterations in the PBP enzymes lead to a decreased affinity between the PBP and the β-lactam drug [37]. However, not all β-lactams bind to the same PBPs. Susceptibility testing should always be done if resistant isolates are identified.

Quinolones. Generally, quinolones inhibit bacterial DNA gyrase and topoisomerase IV, which hinders DNA supercoiling and relaxation, thereby causing bacterial cell death. Mechanisms by which the pneumococci develop resistance to quinolones include target modification (such that increased drug concentrations are needed to obtain the same degree of enzyme inhibition) or active efflux (i.e., pumping drug out of the organism, resulting in lower intracellular concentrations).

Target modification involves 2 stepwise chromosomal mutations in the quinolone resistance–determining region of genes that encode the ParC and ParE subunits of topoisomerase IV *(parC* and *parE)* and the GyrA and GyrB subunits of DNA gyrase (also known as topoisomerase II; *gyrA* and *gyrB)* [38–41]. DNA gyrase is necessary for DNA replication (i.e., separation of DNA strands), and topoisomerase IV is essential for partitioning of replicated chromosomal DNA, which allows it to be packaged within the cell. Topoisomerase IV is a key target for quinolones with activity against gram-positive organisms, including *Staphylococcus aureus* and *S. pneumoniae* [42]; some quinolones also may target DNA gyrase preferentially [43]. The first-step *parC* mutation in topoisomerase IV results in low-level quinolone resistance (ciprofloxacin MIC, 4–8 μg/mL). The second-step mutation in *gyrA* of DNA gyrase results in high-level resistance (ciprofloxacin MIC, 16–64 μg/mL) [44]. Mutations in *parE* and *gyrB* also may be involved in quinolone resistance [45].

Newer quinolones, such as gatifloxacin, gemifloxacin, and moxifloxacin, have enhanced activity against topoisomerase IV

Table 2. Recent global prevalence estimates of penicillin resistance among *Streptococcus pneumoniae*.

Source	Year(s) included	Geographic area	No. of isolates tested	Susceptible isolates,[a] %	Nonsusceptible isolates,[b] %	
					Intermediately resistant	Resistant
CDC [15]	1997	United States	3237	75.0	11.4	13.6
Doern et al. [16]	1997	United States	845	56.2	27.8	16.0
		Canada	202	69.8	21.8	8.4
Doern et al. [17]	1999–2000	United States	1531	65.8	12.7	21.5
Jacobs et al. [18]	1997	United States	1476	49.6	17.9	32.5
Pfaller et al. [19]	1997	United States	341[c]	63.9	25.0	11.1
		Canada	102[c]	72.5	23.6	3.9
		Latin America	32[c]	34.4	56.2	9.4
Schito et al. [3]	1998	Europe	1739	80.9	8.2	10.9
Song et al. [6]	1996–1997	Asia	996	59.0	22.7	18.3

NOTE. CDC, Centers for Disease Control and Prevention.

[a] MIC, ≤0.06 μg/mL.
[b] Either intermediate-level (MIC, 0.12–1.0 μg/mL) or high-level (MIC, ≥2 μg/mL) resistance.
[c] Bloodstream isolates.

and DNA gyrase, so that even organisms with 1 mutation in the *parC* subunit would be susceptible to the drug [40]. Among the newer quinolones that have enhanced activity against *S. pneumoniae,* gemifloxacin appears to be the most active inhibitor of topoisomerase IV in both quinolone-susceptible and quinolone-resistant pneumococcal strains [42].

An active efflux mechanism also may be involved in quinolone resistance in *S. pneumoniae,* generally resulting in lower-level resistance (i.e., a 2–4-fold increase in MICs). This mechanism most likely is mediated by an efflux protein, PmrA, in *S. pneumoniae* [45–47].

Macrolides. Two main mechanisms of macrolide resistance have been described in *S. pneumoniae:* target alteration and active efflux. In the former, expression of a ribosomal methylase encoded by the *ermB* (erythromycin-resistance methylase) gene results in alteration of 23S rRNA subunit target sites. Mutations of this variety, called "MLS$_B$ type" (macrolide–lincosamide–streptogramin B type), are responsible for high-level macrolide resistance and complete cross-resistance to clindamycin [48].

A second mechanism by which *S. pneumoniae* may develop resistance to erythromycin is via an ATP-dependent efflux pump encoded by the *mefE* gene. Resistance to macrolides generated by this mechanism is low level, and organisms remain uniformly susceptible to clindamycin and to the 16-membered macrolides (josamycin and rokitamycin) [48, 49]. *S. pneumoniae* have been isolated that have complete cross-resistance to the newer macrolides, including clarithromycin, dirithromycin, and roxithromycin; the azalide azithromycin; and erythromycin [50, 51]. It should be noted that the higher the penicillin G MIC, the more

Table 3. Prevalence estimates of pneumococcal resistance to commonly used antimicrobial agents in the United States.

Source	Year(s) included	No. of isolates tested	Prevalence of resistance to antimicrobial agent, % of isolates									
			Macrolides[a]	Amox	TMP-SMZ	Quinolones[b]	Cfac	Cfur	Ctax	Cfep	Tet	Vm
Doern et al. [16]	1997	845	11.7–14.3	18.1	19.8	NT	38.3	19.5	4.0	8.2	10.2	0
Doern et al. [17]	1999–2000	1531	26.1–26.2	6.3	35.9	5.6[c]	32.4	27.3	NT	NT	16.6	0
Gay et al. [28]	1999	709	30.7	NT	NT	NT	NT	NT	NT	NT	NT	NT
Hofmann et al. [14]	1994	431	15	NT	26	1[c]	14	NT	9	NT	8	0
Jacobs et al. [18]	1997	1476	30.2–30.8	36.5	NT	16.2[d]	77.6	37.1	NT	NT	NT	NT
Pfaller et al. [19]	1997	341	10.0–10.6	12.3	20.2	NT[d]	NT	16.1	10.6	13.2	NT	0

NOTE. Amox, amoxicillin; Cfac, cefaclor; Cfep, cefepime; Ctax, cefotaxime; Cfur, cefuroxime; NT, not tested; Tet, tetracycline; TMP-SMZ, trimethoprim-sulfamethoxazole; Vm, vancomycin.

[a] Azithromycin, clarithromycin, and erythromycin.
[b] Ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, ofloxacin, and sparfloxacin.
[c] Ofloxacin.
[d] Ciprofloxacin.

likely the strain is to be resistant to macrolides. Recently, ribosomal protein mutations in L4 and 23S rRNA that lead to macrolide resistance have been described [52].

Ketolides are macrolide derivatives composed of a 14-member lactone ring with a 3-keto substitution for the L-cladinose component. Ketolides inhibit protein synthesis by reversibly binding to rRNA. It has been suggested that the absence of L-cladinose in ketolides makes them less likely to induce resistance [53, 54]. Because ketolides have demonstrated activity against macrolide-resistant organisms, in addition to macrolide-susceptible organisms, they have been regarded as a potential alternative to macrolides. However, cross-resistance to the ketolide telithromycin has already been reported in strains of *S. pneumoniae* that were resistant to macrolides [55].

Trimethoprim-sulfamethoxazole. Resistance among *S. pneumoniae* to trimethoprim-sulfamethoxazole is attributed to specific resistance to the trimethoprim component. Specifically, mutations to the dihydrofolate reductase gene lead to reduced affinity of trimethoprim for its target enzyme, dihydrofolate reductase [56].

Tetracycline. The mechanism by which *S. pneumoniae* develop resistance to tetracycline (as well as doxycycline and minocycline) is through alteration in the *tetM* gene. This gene encodes a protein that protects against inhibition of ribosomal protein synthesis by the antibiotic. It is carried on the same transposon as genes that encode proteins providing similar protection against trimethoprim-sulfamethoxazole and chloramphenicol [57, 58].

CAN WE CONTROL THE DEVELOPMENT OF RESISTANCE IN *S. PNEUMONIAE*?

Controlling the spread of resistant pneumococci will require a worldwide multidisciplinary approach involving clinicians, public health officials, epidemiologists, pharmacists, and microbiologists. A study in Iceland demonstrated that recent antibiotic use, residence in an area where overall antibiotic use was high, and treatment with trimethoprim-sulfamethoxazole were significantly ($P < .001$) associated with carriage of penicillin-resistant pneumococci in children [59]. This study supports the suggestion that judicious use and selection of antimicrobials with excellent antipneumococcal activity is important in decreasing the prevalence of resistant *S. pneumoniae*. Information on pharmacokinetics and pharmacodynamics can assist physicians in making appropriate antimicrobial choices.

Pharmacokinetics and pharmacodynamics. Pharmacokinetics is the study of the absorption, distribution, metabolism, and elimination of a drug from the body. Pharmacodynamics is the study of the relationship between drug concentration (in serum or tissue) and the anticipated pharmacological effects (e.g., bacterial killing) at the site of activity. MICs for a particular pathogen may be misleading if they are used as the sole criterion for selecting an antimicrobial agent, because the MIC of a given antimicrobial provides only partial insight into its potency [60–64].

The β-lactams (i.e., penicillins, cephalosporins, and carbapenems), the macrolides, and clindamycin display time-dependent kill rates. Thus, the length of time that the serum concentration of the antimicrobial drug exceeds the MIC value (i.e., time > MIC) is related to bacterial cure rates. In general, if the antimicrobial serum concentration is higher than the MIC for at least 40% or 50% of the dosing interval for penicillins and cephalosporins, respectively, bacteriologic cure rates will be high [62, 63]. A study of mortality associated with *S. pneumoniae* infection in animal models has shown that the survival rate was nearly 0% when serum levels exceeded the MIC for ≤20% of the dosing interval but was 90%–100% when serum concentrations were higher than the MIC value for ≥40%–50% of the dosing interval [63]. Studies of children with acute otitis media [65] and adults with pneumococcal pneumonia have replicated these findings. Most oral β-lactams, with the exception of amoxicillin and, perhaps, cefuroxime, cannot be used to treat acute otitis media caused by penicillin-nonsusceptible *S. pneumoniae*, because the length of time that the drug concentration is higher than the MIC is too short [66].

The aminoglycosides and quinolones display concentration-dependent pharmacokinetic and pharmacodynamic mechanisms, meaning that higher serum concentrations correlate with higher bacterial kill rates. Thus, the key parameter used to

Table 4. Proportions of pneumococcal isolates resistant to penicillin or cefotaxime that were also resistant to other antimicrobial drugs in metropolitan Atlanta, 1994.

Drug	No. (%) of isolates resistant to antimicrobial agent	
	Penicillin	Cefotaxime
Penicillin	—	37 (100)
TMP-SMZ	82 (75)	35 (95)
Cefaclor	59 (54)	25 (68)
Cefotaxime	37 (34)	—
Erythromycin	45 (41)	18 (49)
Tetracycline	26 (24)	14 (38)
Imipenem	25 (23)	24 (65)
Chloramphenicol	13 (12)	9 (24)
Ofloxacin	1 (1)	0 (0)
Multiple drugs	86 (79)	35 (95)
Total	109	37

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole. Reproduced from [14], with permission.

Table 5. Ratios of 24-h area underneath the curve (AUC) to MIC_{90} for *Streptococcus pneumoniae* for selected quinolone antibiotics.

Drug, daily oral dose	Total-drug AUC/MIC ratio	Free-drug AUC/MIC ratio
Levofloxacin, 500 mg	47.5/1.0 (47.5)	29.5–36.1/1.0 (30.0–36.0)
Gatifloxacin, 400 mg	51.3/0.5 (102.6)	41/0.5 (82.0)
Moxifloxacin, 400 mg	48.0/0.25 (192.0)	24.0/0.025 (96.0)
Gemifloxacin, 320 mg	8.4/0.03 (280.0)	2.9–3.8/0.03 (96.7–126.7)

NOTE. Data are from GlaxoSmithKline (Philadelphia) and [60, 67, 68].

predict clinical and bacterial eradication with these antimicrobials is the ratio of the 24-h area under the concentration-time curve (AUC) to the MIC (AUC/MIC ratio, sometimes called "area under the inhibitory curve," or AUIC) [63]. The AUC and thereby the AUC/MIC ratio may be calculated for total drug or free drug. Although most studies have reported total-drug ratios, the free-drug AUC/MIC ratio may be more important. For example, when quinolones were tested, mortality rates among immunocompromised animals were high (>50%) when the AUC/MIC ratio (or AUIC) was <30, and mortality rates were nearly 0% when the AUC/MIC ratio exceeded 100. AUC/MIC ratios of ≥100–125 have been predictive of satisfactory clinical outcome in immunocompromised patients who are receiving intravenous quinolones for serious bacterial infections [61, 63, 64]. In animals with intact immune systems, a free-drug AUC/MIC ratio of 25 may be adequate. At present, there is no real consensus on the ideal target free-drug AUC/MIC ratio for most patients, but data suggest that, for *S. pneumoniae,* a ratio of at least 25–30 and perhaps as high as 55 is necessary (table 5) [63, 67].

The azalide azithromycin, the ketolides, tetracycline, vancomycin, and the streptogramins can be placed in another category. These antimicrobials exhibit time-dependent killing and a prolonged postantibiotic effect [63]. However, these drugs more closely resemble those that exhibit concentration-dependent killing, because the AUC/MIC ratio most closely correlates with therapeutic efficacy.

Although these pharmacokinetic and pharmacodynamic tools are still more theoretical than practical, an understanding of these parameters should help clinicians select appropriate antimicrobial therapy and design an ideal dosing regimen, which is particularly important in light of growing antimicrobial resistance and the need to choose effective empirical therapy [18]. In addition, obtaining local or regional surveillance data on a regular basis, when this is possible, can help in determining the most appropriate therapy. This information can be used in conjunction with published guidelines for treatment of community-acquired pneumococcal pneumonia [69], acute otitis media [70], acute bacterial sinusitis [71, 72], and pneumococcal meningitis [73].

Promotion of pneumococcal vaccine to prevent infections.

The Advisory Committee on Immunization Practices recommends use of a pneumococcal vaccine containing purified capsular polysaccharide from 23 of the most common *S. pneumoniae* serotypes for certain at-risk groups. These groups include (1) persons ≥65 years old whose vaccination status is unknown or who were <65 years old when they were vaccinated but for whom 5 years have passed since vaccination and (2) persons ≥2 years old who are at increased risk of infection because of chronic illness (e.g., cardiovascular, pulmonary, or hepatic illness), functional asplenia, or immune compromise [74]. Unfortunately, current rates of pneumococcal vaccination among adults are low and are substantially lower than the year 2000 national goal of 60%. In 1993, a US immunization survey showed that only 28.2% of people ≥65 years of age had received pneumococcal vaccine [75].

This polysaccharide pneumococcal vaccine is not effective in children <2 years old. A heptavalent conjugate pneumococcal vaccine containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F was recently introduced specifically for use in this population [76]. In a randomized, double-blind trial that included 37,868 healthy infants, the incidence of invasive pneumococcal disease was reduced by 89.1% ($P < .001$) among children who had received at least 1 dose of vaccine [77]. The vaccine also reduced the number of physician visits for otitis media by 8.9% and the number of occasions on which ventilatory tube placement was needed by 20.1%. In a separate study of the same heptavalent pneumococcal vaccine ($n = 1662$), the incidence of otitis media caused by serotypes contained in the vaccine or cross-reactive serotypes (6A, 9N, 18B, 19A, and 23A) was reduced by 57% and 51%, respectively [78]. It is hoped that widespread use of this vaccine in children will not only reduce invasive pneumococcal disease and the rates of otitis media caused by *S. pneumoniae* but also decrease the incidence of infection with drug-resistant *S. pneumoniae*.

CONCLUSIONS

S. pneumoniae is a pervasive and problematic pathogen around the globe because of its resistance to penicillin and other classes of antimicrobials. Controlling the spread of resistant pneumococci through appropriate and judicious prescribing to re-

duce selective pressure is necessary. Appropriate empirical drug choices can be made if local surveillance data are understood and applied in conjunction with the results of susceptibility testing and pharmacokinetic and pharmacodynamic data. Newer quinolones that have better antipneumococcal activity in vitro (e.g., gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) are appealing agents for treatment of adults with community-acquired respiratory infections.

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