Appropriate Use of Antimicrobials for Drug-Resistant Pneumonia: Focus on the Significance of β-Lactam–Resistant *Streptococcus pneumoniae*

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The β-lactam antibiotics (penicillins and cephalosporins) are commonly prescribed for the treatment of community-acquired pneumonia. However, *Streptococcus pneumoniae*, the most common etiologic agent of community-acquired pneumonia, has become increasingly resistant to β-lactams over the past decade. The results of several studies suggest that penicillins remain effective for streptococcal pneumonia when the infecting pathogen has a minimal inhibitory concentration (MIC) ≤2 μg/mL, presumably because the pharmacokinetic and pharmacodynamic parameters associated with current dosing regimens are still sufficient. However, when the MIC ≥4 μg/mL, increased rates of mortality (for patients who survive their first 4 days of hospitalization) may occur. Currently, 3.5%–7.8% of *S. pneumoniae* clinical isolates have MICs that fall in this latter class, but these rates may rise in the future. The clinical relevance of in vitro resistance may be related to at least 3 factors: concordance of antimicrobial therapy, severity of illness, and virulence.

Despite an awareness of increasing numbers of pathogens associated with community-acquired pneumonia (CAP), *Streptococcus pneumoniae* remains the most common etiologic agent of this disease. In a meta-analysis of 122 reports of CAP in the English-language literature for 1966–1995, *S. pneumoniae* accounted for two-thirds of >7000 cases in which an etiologic diagnosis was made, as well as for two-thirds of the cases associated with mortality [1]. The mortality from pneumococcal pneumonia, which remains unchanged in the past decade despite effective antimicrobial therapy, is ~10% for patients with nonbacteremic pneumonia. It is higher for patients with bacteremic pneumonia or severe pneumonia and for patients who are elderly [2].

Empirical therapy for CAP has been complicated by the emergence of antimicrobial resistance of the pneumococcus over the past decade and by the concern for other etiologic agents, such as pathogens associated with atypical pneumonia [3, 4]. This review will examine the clinical significance of penicillin-resistant *S. pneumoniae*, particularly in cases where penicillins or cephalosporins are the chosen antimicrobial. In addition, it will describe the challenges associated with choosing empirical antimicrobials in this era of increasing drug resistance.

EMERGENCE OF RESISTANT *S. PNEUMONIAE*

Before the early 1990s, clinical isolates of *S. pneumoniae* were nearly uniformly susceptible to penicillin. Rare strains of the pneumococcus had been documented with only "intermediate" levels of penicillin susceptibility (MIC 0.1–1 μg/mL), but the majority of clinical isolates were inhibited by levels of penicillin <0.1 μg/mL. For patients with pneumococcal infections who were not allergic to penicillin, this was clearly the drug of choice.

Drug-resistant *Streptococcus pneumoniae* (DRSP)

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strains, however, have steadily increased in prevalence. DRSP were identified in New Guinea as early as 1967 [5], but medical experts at the time concluded that the microorganisms were not likely to spread and thus posed little threat to the general population, a prediction that turned out to be false. Pneumococcal infections with strains having increasing MICs became prevalent in South Africa in the 1970s and in Europe in the 1980s. These strains became increasingly prevalent in the United States in the 1990s [6–9]. As an example, in a large-scale surveillance study conducted from December 1997 to May 1998, Thornsberry and colleagues [6] collected 4148 isolates of *S. pneumoniae* from a variety of geographical regions in the United States. By using National Committee for Clinical Laboratory Standards interpretive criteria, they found that 65.1% ($n = 2699$) of the isolates displayed full susceptibility (MIC $\leq$0.06 μg/mL), 22.1% ($n = 915$) displayed intermediate resistance (MIC 0.12–1.0 μg/mL), and 12.8% ($n = 534$) displayed full resistance (MIC $\geq$2.0 μg/mL) to penicillin. In another study, Doern and colleagues [7] evaluated 1531 clinical isolates of *S. pneumoniae* collected from 33 US medical centers during winter 1999–2000. Of these isolates, 34.2% were penicillin nonsusceptible (MIC $\geq$0.12 μg/mL) and 21.5% were high-level resistant (MIC $\geq$2 μg/mL). These rates represent a significant increase from a similar surveillance study of the same investigators during 1994–1995 (penicillin nonsusceptible and high-level resistance were 23.6% and 9.5%, respectively, at that time).

The global emergence of DRSP has most likely occurred in stages that involved selection of resistant mutants and clonal expansion [10]. Many studies suggest that the increase in DRSP is a result of the selective pressure generated by antimicrobial therapy [11–13]. Consistent with this model, Campbell and Silberman [14] found that risk factors for DRSP included recent hospitalization, residence in an institution, extremes of age (particularly <6 years of age), attendance at a day-care center, presence of underlying disease, HIV infection, and immunosuppression.

Given this cause-and-effect relationship between antimicrobial use and resistance, it might be expected that treatment of pneumococcal infections with penicillins and several cephalosporins would be less effective against resistant variants. Although this is true for some types of pneumococcal infections (otitis media and meningitis), it appears to be more controversial for others (pneumonia and bacteremia).

CLINICAL RELEVANCE OF DRSP

Pneumococcal otitis media and meningitis. Treatment of certain types of pneumococcal infections is well documented to be affected negatively by the underlying susceptibility of the pathogen. Dagan and colleagues [15, 16] found that infections of children with acute otitis media caused by nonsusceptible *S. pneumoniae* (penicillin MIC >0.1 μg/mL) had increased rates of treatment failure with selected orally administered cephalosporins and macrolides. Moreover, a variety of authors have shown that children with meningitis caused by nonsusceptible strains of *S. pneumoniae* have higher rates of therapeutic failure when treated with penicillin or third-generation cephalosporins [17–22]. Thus, β-lactam antimicrobials should be chosen with care, particularly when treating meningitis, especially in geographic areas with a high prevalence of penicillin-resistant *S. pneumoniae.* As a consequence of the concern for β-lactam–resistant *S. pneumoniae* in meningitis, the present standard of care is combination therapy with vancomycin and cefotaxime or ceftriaxone as initial therapy for all children 1 month of age or older with definite or probable bacterial meningitis.

CAP. Although there is compelling evidence that drug-resistant pneumococci affect clinical outcomes in patients with meningitis and otitis media, the clinical relevance of resistance in the therapy of nonmeningeal pneumonia infections remains controversial. As will be described below, much of the controversy relates to the interpretation of the breakpoint classification of the pneumococcus for susceptibility and resistance. The National Committee for Clinical Laboratory Standards currently defines the susceptibility of pneumococcus isolates to penicillin as susceptible, <0.06 μg/mL; intermediate, 0.1–1 μg/mL; and resistant, >2 μg/mL [23].

Penicillin-resistant* S. pneumoniae *and CAP-intermediate isolates. Several studies have compared the response of CAP caused by penicillin-susceptible and penicillin-intermediate *S. pneumoniae* to β-lactam therapy. An early study carried out by Friedland and Klugman [24] examined a pediatric population admitted to a general hospital between 1989 and 1991. Eighty-three children with nonsusceptible pneumococcal bacteremia or meningitis were compared with 124 children infected with susceptible strains. The results showed that the sites of infection, underlying diseases, and mortality of patients with penicillin-resistant infections outside the CNS did not differ significantly from those of penicillin-susceptible infections.

Friedland [20] conducted a subsequent prospective, non-interventional study to compare the clinical response in penicillin-nonsusceptible vs. penicillin-susceptible bacteremic pneumococcal infections. After 48 h of therapy, 64% of penicillin-susceptible infections showed improvement versus 60% of penicillin-nonsusceptible infections (OR, 1.2; 95% CI, 0.5–3.0). In children with pneumonia treated with ampicillin or an equivalent β-lactam agent, 93% with penicillin-susceptible infections had improved by day 7 of therapy, compared with 88% with penicillin-nonsusceptible infections (OR, 1.9; 95% CI, 0.3–15.9). The duration of respiratory distress, fever, and oxygen requirement were similar in penicillin-susceptible and -nonsusceptible infections.

In a third study, Pallares and colleagues [25] conducted a 10-year prospective analysis of 504 adults with culture-proved

pneumococcal pneumonia. After the exclusion of patients with polymicrobial pneumonia and adjustment for other predictors of mortality, the OR for mortality in patients with penicillin-nonsusceptible strains was 1.0 (95% CI, 0.5–1.9; $P = .84$). Among patients treated with penicillin or ampicillin, the mortality was 25% in the 24 with penicillin-nonsusceptible strains and 19% in the 126 with penicillin-susceptible strains ($P = .51$). Among patients treated with ceftriaxone or cefotaxime, the mortality was 22% in the 59 with penicillin-nonsusceptible strains and 25% in the 127 with penicillin-susceptible strains ($P = .64$). The mortality rates observed may in part be influenced by the inclusion of patients with nosocomially acquired infection.

Choi and Lee [26] retrospectively analyzed 106 cases of invasive pneumococcal infections diagnosed 1985–1996. Initial empirical regimens were of parenteral β-lactam antimicrobials with or without an aminoglycoside. The types of infection were bacteremia without focus (45%), meningitis (19%), peritonitis (17%), pneumonia (bacteremic, 16%), and others (3%). Among the 72 nonmeningeal infections analyzed, a favorable response at 72 h was observed in 83% of the 40 penicillin-susceptible infections, 86% ($P = 1.0$) of the 14 penicillin-intermediate infections, and 61% ($P = .7$) of the 18 resistant infections. Similarly, the mortality rate was 2.5% in the patients with susceptible infections, 7.1% ($P = .45$) in the patients with intermediate infections, and 11% ($P = .22$) in the patients with resistant infections.

Finally, Deeks and colleagues [27] conducted a retrospective study of hospitalized children ≤5 years of age who had *S. pneumoniae* isolated from a normally sterile site during June 1993–October 1996. Of the 274 children whose records were available for review, 99 (36%) had penicillin-nonsusceptible *S. pneumoniae*. Of these 99, 46 were infected with isolates showing intermediate susceptibility, and 53 were infected with isolates showing high-level resistance. Among children with nonmeningeal invasive disease, there were no significant differences in the response to therapy (including response to penicillin or ampicillin), course of illness, or clinical outcome between children infected with penicillin-susceptible and those with penicillin-resistant isolates.

The preceding studies might be taken to suggest that the levels of penicillin resistance in *S. pneumoniae* have little effect on therapeutic outcome in pneumonia and bacteremia. However, a review from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group (DRSPTWG) argues for more caution [28]. They point out that the majority of nonsusceptible isolates examined in the previous studies fell into the intermediate class (MIC 0.12–1.0 μg/mL). Although some reports of poor outcome among patients infected with intermediate susceptibility strains do exist in the literature [29–31], most evidence indicates standard treatment with a β-lactam antimicrobial is effective against pneumococcal pneumonia caused by strains with penicillin MIC <2 μg/mL. The same may not be true for isolates with higher MICs (see below).

Penicillin-resistant* S. pneumoniae *and CAP–high-resistance isolates. The development of high-level penicillin resistance in *S. pneumoniae* is a stepwise process involving multiple penicillin binding proteins. In the surveillance study by Thornsberry and colleagues [6], 3.1% of the collected *S. pneumoniae* isolates had MIC values of 4 μg/mL and 0.4% had MIC values of ≥8 μg/mL. Other studies have reported as much as 7.8% of isolates with MICs of 4.0 μg/mL or higher [32]. It is prudent to anticipate that these variants, which were once extremely rare, may continue to increase in prevalence with increasing use of antimicrobials. How do infections caused by these strains respond to penicillin therapy?

Feikin and colleagues [32] analyzed the epidemiologic factors affecting mortality from pneumococcal pneumonia during 1995–1997. In the 5837 patients studied, increased mortality was associated with older age, underlying disease, Asian race, and residence in Toronto/Peel, Ontario. When these factors were controlled for, increased mortality was not associated with resistance to penicillin. However, when deaths during the first 4 hospital days were excluded, mortality was significantly associated with penicillin MIC ≥4.0 μg/mL or cefotaxime MIC ≥2.0 μg/mL (table 1). These data argue that patients who died during the first 4 days of hospitalization experienced infections so severe that they were refractory to antimicrobial therapy.

In another study, Turett and colleagues [33] retrospectively analyzed cases of pneumococcal bacteremia (~90% had pneumonia as the source) identified in a large inner-city hospital the 5-year period January 1992–December 1996. Overall, 462 cases of pneumococcal bacteremia were identified in 432 patients. Multivariate analysis showed that high-level penicillin resistance, older age, severe disease, multilobar infiltrates and effusion on chest roentgenogram, and Hispanic ethnicity were independent predictors of mortality in pneumococcal bacteremia. Therefore, as in the study of Feikin et al. [32], these data indicate that caution is warranted when treating pneu-

Table 1. Relative risk of mortality in patients with community-acquired pneumonia treated with β-lactam antimicrobials [32].

Antimicrobial	Adjusted OR[a]	95% CI
Penicillin		
MIC ≥4 μg/mL	7.1	1.7–30.0
MIC 0.1–1.0 μg/mL	1.0	0.3–3.0
Cefotaxime		
MIC 1 μg/mL	1.2	0.3–7.4
MIC >2 μg/mL	5.9	1.1–33.0

[a] Adjusted after day 4 for age, geographical location, and underlying disease.

mococcal bacteremia caused by highly penicillin resistant variants of *S. pneumoniae.*

Metlay and colleagues [34] examined the impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia in a retrospective cohort study conducted in 1994. Of the 192 study patients, 44 (23%) were infected with pneumococcal strains that demonstrated some degree of penicillin nonsusceptibility (unfortunately, the study did not report on a cohort of patients with MIC ≥ 4 μg/mL). Compared with patients infected with penicillin-susceptible pneumococcal strains, patients whose isolates were nonsusceptible had a significantly greater risk of in-hospital death due to pneumonia (RR, 2.1; 95% CI, 1–4.3) and suppurative complications of infection (RR, 4.5; 95% CI, 1–19.3; figure 1). Only the risk of suppurative complications remained statistically significant after adjustment for baseline differences in severity of illness.

Not all studies have found that high penicillin resistance has clinical significance, however. For instance, Ewig and colleagues [2] determined the incidence of and risk factors for drug resistance of *S. pneumoniae,* as well as its impact on outcome in hospitalized patients with CAP. A total of 101 patients were examined, 79 of whom were immunocompetent and 22 immunosuppressed. Among the immunocompetent patients, 5 were infected with penicillin-resistant *S. pneumoniae* (MIC ≥ 2 μg/mL), whereas among the immunocompromised patients, 9 had resistant isolates. When comorbidities, age, and other factors were controlled, penicillin resistance was found not to be significantly associated with mortality (RR, 2.5; 95% CI, 0.7–8.9; $P = .14$). It is important to note, however, that this study also failed to report the number of infecting pathogens with MIC ≥ 4 μg/mL.

Limitations of available studies. For many of these studies, a number of confounding variables other than specific MIC of the pathogen may influence outcome measurements, including age, underlying disease, and duration and extent of illness at the start of therapy. In addition, several of the reports fail to specify the drug regimen followed by the patients, which again limits interpretation of the results. Randomized prospective clinical trials will ultimately be required to unambiguously determine the clinical significance of DRSP.

The clinical relevance of in vitro resistance may be related to at least 3 factors associated with the clinical isolate: concordance of antimicrobial therapy, severity of illness, and virulence [34]. The first factor, concordance, considers the antimicrobial therapy received by the patient in relation to the in vitro susceptibility. Intuitively, an agent that is active in vitro should be associated with a better clinical outcome than one for which the pathogen is "resistant." With the exception of the observational studies previously reviewed, it is currently difficult to test this effect because the majority of patients now receive regimens for CAP that are active against penicillin-resistant *S. pneumoniae.* The use of third-generation cephalosporins (which also have greater activity against *S. pneumoniae* than penicillin) and fluoroquinolones reduce the likelihood of discordant therapy for *S. pneumoniae.* An analysis of 3 studies finds only 20 patients with discordant therapy, and the clinical outcome did not seem to correlate with this factor (table 2).

Confounding variables, such as comorbid conditions that independently affect clinical outcome, are other significant considerations for clinical outcome. Several studies have linked clinical and patient factors to the outcome, as well as to the predisposition for having resistant isolates of pneumococcus [1, 2]. Thus, it is not surprising that these confounding variables themselves often overpower the effect of specific antimicrobial therapy [25].

A controversial factor for consideration of clinical outcome is any potential relation of virulence and antimicrobial susceptibility. The use of animal models to predict the impact of β-lactam resistance on the clinical outcome of pneumonias has

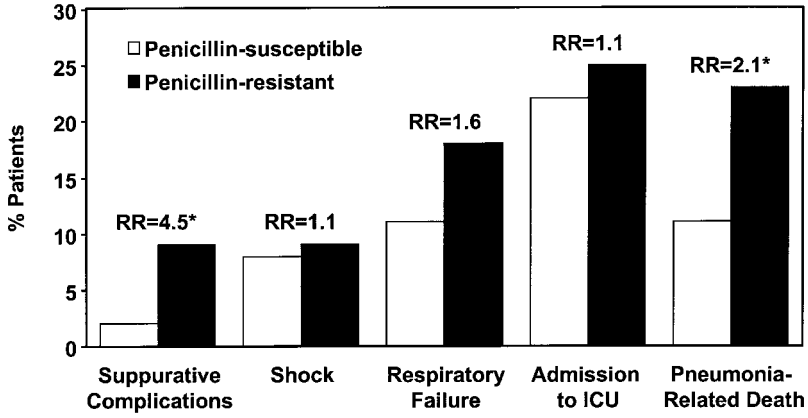

Figure 1. Outcomes for hospitalized patients with pneumococcal pneumonia ($n = 192$) [34]. Only suppurative complications remained statistically significant when adjusted for other risk factors (see text). RR, unadjusted relative risk, Cochran-Mantel-Haenszel statistics; *, statistically significant.

Table 2. Effect of discordant therapy in the treatment of drug-resistant *Streptococcus pneumoniae*.

Study	Mortality rate, %	
	Concordant therapy	Discordant therapy
Pallares et al. [25]		
Penicillin	19	25
Cephalosporin	25	22
Ewig et al. [2]		
Penicillin-cephalosporin	10	12
Metlay [34][a]	14	11

[a] Specific antimicrobial agents not indicated.

been hampered by the difficulty in finding multiresistant isolates that are able to cause pneumonia in an animal model. Much of the useful clinical data have relied on animal models such as the neutropenic thigh infection model. However, Berry and colleagues [35] have identified multiresistant pneumococci that are able to cause pneumonia in a rat model. Bactericidal activity (>3 logs of killing) was demonstrated by using amoxicillin-clavulanate against a pneumococcal strain with an amoxicillin MIC of 2 μg/mL. This antibiotic was not able to reliably produce a bactericidal effect when the infecting strain had an amoxicillin MIC of 8 μg/mL. Although the issue of virulence related to antimicrobial resistance is unclear (especially in animal models), there is an abundance of evidence in the literature demonstrating the virulence of antibiotic-resistant pneumococci in humans [36]. Thus, it seems prudent at present to consider penicillin-resistant *S. pneumoniae* to be virulent pathogens.

PHARMACODYNAMIC CONSIDERATIONS AND TREATMENT GUIDELINES

In addition to the clinical studies, pharmacokinetic and pharmacodynamic considerations suggest that β-lactam therapy would be effective against pneumococcal strains with intermediate susceptibility to penicillin. The critical determinant of success for β-lactam antimicrobials is the duration of time that serum or tissue levels exceed the MIC; optimal success is observed when the free-drug concentration is above the MIC for at least 40%–50% of the dosing interval [37]. To achieve these conditions for adult streptococcal pneumonia caused by an intermediate-resistance pathogen, 8 million to 15 million units of penicillin G given daily in 4–6 divided doses appears to be effective [37, 38]. In children, dosages ranging from 100,000 to 300,000 U/kg per day in 4–6 divided doses appear to be effective [26, 27, 39, 40]. Unsuccessful treatment of drug-resistant otitis media and meningitis by the same regimens probably reflects the difficulty of drug accumulation in middle ear fluid, which acts as a closed-space site of infection, or in CSF, which is segregated by the blood-brain barrier.

Variability exists among the various parenteral β-lactams in regard to their abilities to attain a pharmacokinetic-pharmacodynamic parameter target of time (T) > MIC 40% for drug-resistant pneumococcal strains. For example, among the cephalosporins, ceftriaxone, cefotaxime, and cefepime would all produce $T > MIC_{90} > 40\%$ (range, 87%–100%) against *S. pneumoniae.* Cefuroxime just hits the 40% target, whereas ceftazidime and cefazolin attain $T > MIC_{90}$ of only 32% and 20%, respectively. Similarly, among the remaining β-lactams, penicillin and ampicillin at standard dosing achieves $T > MIC_{90}$ far exceeding 40%, whereas ticarcillin does not (23%) [37, 41].

RECOMMENDATIONS OF THE DRSPTWG

Studies such as those described in this review led the DRSPTWG to recommend alterations to the susceptibility categories when treating pneumonia [28]. Specifically, they recommended that penicillin susceptibility in *S. pneumoniae* be defined as an MIC ≤1 μg/mL, intermediate susceptibility be defined as an MIC of 2 μg/mL, and resistance be defined as an MIC ≥4 μg/mL (this also applies to cefotaxime and ceftriaxone). These values are more clinically relevant for pneumonia because according to these breakpoints, treatment failures are associated only with fully resistant strains. It is important to note that these changes in breakpoints pertain only to streptococcal pneumonia. Because of their clinical utility when treating otitis media and meningitis, it was recommended that the original breakpoints remain in effect for the latter diseases.

Thus, interpretation of present data suggests that CAP caused by isolates of *S. pneumoniae* presently considered as intermediately resistant (MIC 0.1–1.0 μg/mL) should respond well to treatment with a β-lactam agent used in appropriate doses. Therapeutic failures are more likely to occur at higher levels of resistance (MIC >2 μg/mL).

MULTIDRUG-RESISTANT *S. PNEUMONIAE*

Penicillin resistance is only part of the picture with DRSP. Multicenter surveillance studies document isolates that are resistant to penicillin and other classes of drugs, including other β-lactams (such as cephalosporins), macrolides, sulfa/trimethoprim, tetracyclines, and chloramphenicol [42, 43]. Resistance to the macrolides is of significant concern because of their common use for empiric therapy of respiratory infections, including those caused by *S. pneumoniae.*

A close correlation is found between β-lactam resistance and macrolide resistance. This is not because the genes encoding resistance are linked but because resistant determinants are selected in the same environment, and additive selective de-

terminants confer selective advantage to those strains each time they are exposed to antibiotics. Resistance extends beyond the β-lactam antibiotics. Organisms resistant to β-lactams often have acquired genes that confer resistance to other classes of antimicrobials. Table 3 shows the relative activities of a variety of commonly used antimicrobials against *S. pneumoniae,* stratified by susceptibility to penicillin.

CHOOSING AN APPROPRIATE EMPIRICAL ANTIMICROBIAL

Although *S. pneumoniae* is the most common etiological agent of CAP, a diverse array of other gram-positive, gram-negative, and atypical pathogens can cause this disease. Because culture results are rarely available before the onset of therapy, antimicrobial choice is typically empirical. The issue for the prescribing clinician, therefore, is not only a concern for DRSP, but also for other pathogens, which increases the challenge for appropriate therapy.

As indicated by Bryan et al. [38], "therapy of pneumococcal pneumonia is at a crossroads." Although penicillin G has been the drug of choice for CAP in the past, there is a widespread impression that this drug is now seldom used for this disease. Broader-spectrum antibiotics are favored because of the multiple potential etiologies. Rising concerns about penicillin-resistant pneumococci may prompt therapy with newer cephalosporins, newer fluoroquinolones, or even vancomycin for suspected or proven pneumococcal disease. Moreover, invasive pneumococcal disease resistant to third-generation cephalosporins as well as other classes of drugs (i.e., macrolides) are now being reported. When pathogens become increasingly resistant to antimicrobial agents, therapeutic choices are limited and pose potential threats to patients. In addition, the emergence of resistant pathogens often exerts additional selective pressure on any antimicrobial that remains effective. Because *S. pneumoniae* infections are so common, the awareness of DRSP has led to an increase in the use of agents such as vancomycin, and therefore threatens resistance to this agent as well.

As pointed out by Kollef and Ward [44], a clear consensus on how drug resistance should influence the choice of antimicrobial remains elusive. Clinicians may find it "safe" to assume that every infection is caused by a drug-resistant pathogen and choose antimicrobials accordingly. However, if antimicrobial use is liberalized too far, it may promote the emergence of even more multiresistant organisms. Thus, the challenge is to determine the prevalence of antimicrobial resistance that makes it necessary to include coverage of resistant organisms in empiric regimens. The answer will require large-scale epidemiological studies that track the rates of treatment failures and compare them to underlying levels of drug-resistant pathogens in the community.

Table 3. Susceptibility of *Streptococcus pneumoniae* to commonly used antimicrobial agents, stratified by susceptibility to penicillin [3].

	Susceptibility to indicated agent, MIC of penicillin		
Agent	≤0.1 μg/mL	0.1–1.0 μg/mL	≥2 μg/mL
Amoxicillin	+++	+++	+
Doxycycline	+++	+	+/−
Macrolide[a]	+++	+	+/−
Clindamycin	+++	++	+
TMP-SMZ	++	−	−
Cefuroxime	+++	+	−
Cefotaxime	+++	+++	+
Fluoroquinolone[b]	+++	+++	+++
Imipenem	+++	+++	−
Vancomycin	+++	+++	+++

NOTE. In the MIC categories, the estimated percentages of pneumococci covered by the indicated agents are represented as follows: +++, ≥90%; ++, ≥75%; +, ≥50%; +/−, ≥40%; and −, <40%. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Erythromycin, clarithromycin, or azithromycin.

[b] Fluoroquinolone with improved activity against *S. pneumoniae* (e.g., levofloxacin, grepafloxacin, or trovafloxacin).

At the present time, management of initial antimicrobial choice is often suboptimal, even for susceptible cases of CAP. Ewig and colleagues [2] evaluated the routine management of patients with CAP with regard to severity patterns, diagnostic approaches, and results [45]. Particularly germane to this discussion, they also examined how initial empiric antimicrobial treatment affected outcome. Two hundred thirty-two consecutive patients with CAP admitted to a primary-care hospital were studied prospectively. Patients were classified according to Fine's severity score [46], and diagnostic approaches and initial antimicrobial treatment were judged according to the guidelines of the European Respiratory Society [47]. CAP infections were categorized as follows: 55 (24%) were mild, 156 (67%) were moderate, and 21 (9%) were severe. Inadequate initial antimicrobial treatment was significantly more frequent in severe (18 [86%] of 21) than in mild (5 [9%] of 55) and moderate CAP (39 [25%] of 156; $P = .0001$). Conversely, antimicrobial overtreatment occurred significantly more often in mild (30 [55%] of 55) and moderate (77 [49%] of 156) than in severe CAP (0 [0%] of 21; $P = .0001$). Inadequate initial antimicrobial treatment was more frequent in nonresponders (18 [29%] of 62 vs. 31 [18%] of 170; RR, 1.6; 95% CI, 0.9–2.6; $P = .07$) and was associated with a longer duration of hospitalization (17 ± 11 vs. 14 ± 8 days; $P = .03$).

Beyond these issues of adequate therapy, some information in the literature suggests that the initial choice of empiric antimicrobial can also influence therapeutic outcome. For example, Gleason and colleagues [48] determined the associations

between initial antimicrobial therapy and 30-day mortality in hospitalized elderly patients with pneumonia. To do so, they reviewed the hospital records of 12,945 Medicare inpatients (≥65 years of age) with pneumonia, focusing in part on the relationship between initial antimicrobial choice and 30-day mortality by Cox proportional hazards models. The models were adjusted for baseline characteristics, illness severity, and process of care. Compared with a nonpseudomonal third-generation cephalosporin alone (the reference antimicrobial), initial treatment with a second-generation cephalosporin plus macrolide, a nonpseudomonal third-generation cephalosporin plus macrolide, or a fluoroquinolone alone were independently associated with lower 30-day mortality rates (table 4). Adjusted mortality among patients initially treated with these 3 regimens became significantly lower beginning 2, 3, and 7 days after hospital admission, respectively. By comparison, use of a β-lactam/β-lactamase inhibitor plus macrolide and an aminoglycoside plus another agent were associated with an increased 30-day mortality.

In the absence of hard and fast rules, various guidelines can help clinicians deal with antimicrobial choice vis-à-vis drug resistance [44]. First, it is important to be familiar with local resistance patterns. Second, microbiology results, particularly susceptibility tests, should be used to narrow the choice of suitable antimicrobials. Third, to avoid further spread of antimicrobial resistance, it is important to use optimal dosing regimens. Fourth, rapid and random switches of antimicrobials, so-called antibiotic surfing, should be avoided. Fifth, hospital infections in general should be controlled to the greatest extent possible. Finally, each institution should establish restrictions and guidelines for antimicrobial use.

RECOMMENDATIONS OF RECENT GUIDELINES

The selection of specific antimicrobial regimens for empirical therapy in recently published guidelines from North America is based largely on the most likely pathogens for CAP, the in vitro activities of commonly used antimicrobials, and completed clinical studies [3, 4]. Clearly, all of the guidelines indicate that *S. pneumoniae* is the single most important pathogen in CAP. Therefore, the potential for antimicrobial resistance exhibited by this pathogen has a significant impact on recommended therapy.

EMPIRICAL THERAPY

Outpatients. Both of the new North American guidelines variably recommend macrolides, doxycycline, or an antipneumococcal fluoroquinolone as treatment options for empirical therapy of outpatients with CAP. The rationale is to provide coverage of *S. pneumoniae* (including possible DRSP) and the atypical pathogens (most commonly *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) that have been shown to be prevalent as causative agents in epidemiological studies in North America. Because there is no convincing association between individual symptoms and physical findings with specific etiology, the rationale is to direct the initial empirical therapy toward these most likely causes.

In the Canadian statement [4], outpatients are stratified into those without modifying factors, for whom a macrolide may be used, and those with modifying factors (such as chronic obstructive lung disease or the recent use of antibiotics or steroids, for whom DRSP is of greater concern). Fluoroquinolones are considered appropriate for the latter group. The Infectious Diseases Society of America statement [3] indicates that the selection considerations among the 3 options should be influenced by regional antibiotic susceptibility patterns for *S. pneumoniae* and the presence of risk factors for DRSP (such as the use of antimicrobial agents within the previous 3 months). The statement further indicates that "for older patients or those with underlying disease, a fluoroquinolone may be a preferred choice; some authorities prefer to reserve fluoroquinolones for such patients." The Centers for Disease Control and Prevention statement is similar but stresses that fluoroquinolones should be reserved for cases associated with failure or allergy to other agents or cases caused by documented DRSP. The rationale is

Table 4. Independent associations between initial antimicrobial therapy and 30-day mortality [48].

Initial antimicrobial regimen	Hazard ratio (95% CI)[a]
β-Lactam/β-lactamase inhibitors plus macrolides	1.77 (1.28–2.46)
Aminoglycosides plus any other antimicrobial agent	1.21 (1.02–1.43)
Macrolides only	1.06 (0.69–1.61)
Nonpseudomonal third-generation cephalosporins only	Reference group
Nonpseudomonal third-generation cephalosporins plus macrolide	0.74 (0.60–0.92)
Second-generation cephalosporin plus macrolide	0.71 (0.52–0.96)
Fluoroquinolones alone	0.64 (0.43–0.94)

[a] Thirty-day mortality rate.

that the fear of widespread use may lead to the development of fluoroquinolone resistance among the respiratory pathogens, as well as other pathogens colonizing patients.

Inpatients. Both of the North American revised guidelines recommend treatment with either combination therapy of a β-lactam plus a macrolide or monotherapy with a fluoroquinolone. The preferred β-lactam is one that has predicted activity against most *S. pneumoniae* that display intermediate resistance to penicillin. This would include cefotaxime, ceftriaxone, cefepime, and possibly cefuroxime, depending on local susceptibility patterns (although cefuroxime is less active than the other agents listed). The rationale for recommending these regimens is based on studies showing their association with a significant reduction in mortality, compared with administration of cephalosporin alone [48].

PATHOGEN-DIRECTED THERAPY

Treatment options are obviously simplified if the etiologic agent is established. In such cases, antibiotic decisions should be based on in vitro susceptibility tests. As indicated in the Infectious Diseases Society of America guidelines [3], recommended antimicrobial agents for therapy of pneumococcal pneumonia caused by strains with MIC <2 μg/mL include amoxicillin, cefuroxime axetil, cefpodoxime, cefprozil, azithromycin, clarithromycin, the fluoroquinolones, or doxycycline. Amoxicillin is preferred over penicillin because of more reliable absorption, longer half-life, and slightly more favorable MIC. In light of surveillance studies indicating increasing resistance to the macrolides, as well as reports of clinical failure, there is concern about the reduced efficacy of macrolides. For strains with MIC >2 μg/mL, agents should be based on specific in vitro susceptibility tests. Potential β-lactam choices include cefotaxime and ceftriaxone. Fluoroquinolones and vancomycin are other alternatives. The ketolides may offer additional options for outpatients, particularly because they are not available for parenteral administration.

In hospitalized patients, pneumococcal pneumoniae caused by organisms that are susceptible or intermediately resistant to penicillin responds to treatment with penicillin (2 million units q4h), ampicillin (1 g q6h), cefotaxime (1 g q8h), or ceftriaxone (1 g q24h). Pneumonia due to penicillin- or cephalosporin-resistant organisms requires higher doses of these drugs. For isolates with penicillin or cephalosporin MIC >4 μg/mL, a fluoroquinolone or vancomycin should be used on the basis of susceptibility tests. Quinupristin-dalfopristin or linezolid are other options, but clinical experience with these agents for pneumococcal pneumonia is limited.

ECONOMIC IMPACT OF DRUG RESISTANCE

With the advent of managed care, economic considerations now play a major role in determining how health care services are delivered. These considerations have led, for instance, to the adoption of CAP critical pathways [49], which are therapeutic treatment algorithms that can result in decreased cost without a negative impact on patient outcome [50]. However, determining the economic impact of drug resistance can be a problem [51], although a reasonable estimate is that $4 billion of extra cost was incurred from drug-resistant pathogens in 1995 [52]. These additional costs can arise from prolonged hospitalization, microbiology laboratory procedures, the use of more expensive drugs and combination therapy, and the complications and treatment failures associated with drug-resistant infections. Unfortunately, it is likely that these costs will continue to rise in parallel with an increase in the frequency of highly resistant pathogens. It is hoped that improving how doctors and patients use antimicrobial agents may slow these trends in the future.

SUMMARY

Because of the high penetration of β-lactam antimicrobials into lung tissue, penicillin and cephalosporin treatment of CAP remains effective for *S. pneumoniae* infections with MIC ≤2 μg/mL (by current estimates, ~95% of clinical isolates fall into this range). However, for infections caused by highly resistant pathogens (MIC ≥4 μg/mL for penicillin; MIC >2 μg/mL for cefotaxime), β-lactam therapy may lead to a statistically significant rise in treatment failures. Under these conditions, alternatives to β-lactams may be required. The DRSPTWG recommends fluoroquinolones for infections caused by *S. pneumoniae* with penicillin MIC ≥4 μg/mL [28]. To factor in drug resistance when treating CAP, it is recommended that clinicians familiarize themselves with local resistance patterns and obtain and use microbiology results, particularly susceptibility tests, to narrow antimicrobial choice. Evidence exists that in today's medical climate antimicrobials are not administered judiciously. This practice can result in suboptimal treatment outcomes for patients and further increases in highly resistant respiratory pathogens. Finally, use of the *Streptococcus* vaccine is encouraged to reduce the burden of pneumococcal disease within the community.

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