Microbiological and Pharmacodynamic Considerations in the Treatment of Infection Due to Antimicrobial-Resistant *Streptococcus pneumoniae*

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The incidence of antimicrobial-resistant strains of *Streptococcus pneumoniae* has increased alarmingly in recent years. The problem is exacerbated by the global spread of resistant organisms. Currently, the incidence of penicillin-resistant pneumococci isolated from clinical specimens in the United States is >35%. For empirical oral treatment of community-acquired respiratory infections, 3 choices are available: β-lactam agents, macrolides, and fluoroquinolones. In considering the therapeutic efficacy of these agents, it is essential to also take pharmacokinetic and pharmacodynamic (PK/PD) factors into account. Many drugs are effective against penicillin-susceptible strains. However, the higher the minimum inhibitory concentration of penicillin, the more likely that cross-resistance to β-lactam agents and macrolides will occur. Currently, the incidence of fluoroquinolone-resistant pneumococci is low; it is proposed that adequate dosing based on the PK/PD properties of fluoroquinolones may help reduce the emergence of resistant organisms. Prudent use of all antimicrobials is essential to decrease the emergence of strains resistant to these agents.

The emergence of penicillin-resistant strains of *Streptococcus pneumoniae* was first documented in the late 1960s and early 1970s, with reports from the United States, New Guinea and Australia, and England [1–4]. In South Africa, systematic testing with crude disk susceptibility methods led to the discovery of drug-resistant *S. pneumoniae* (DRSP) that had reduced susceptibility to ≥1 β-lactam and non-β-lactam antibiotic agents [5, 6].

The spread of multidrug-resistant DRSP clonal types, such as the Spanish clone (serotype 23F), variants of the Spanish clone (serotypes 19A, 19B, and 19F), and the Spanish/French clone (serotypes 9 and 14), was recently documented in Europe, Asia, and North America [7] as well as in Latin America [8]. The incidence of DRSP in the United States has been difficult to gauge because of the large geographic area and population. Surveillance studies in the United States, however, indicate that ~20%–40% of lower respiratory tract isolates of *S. pneumoniae* have reduced penicillin susceptibility (MIC, ≥0.12 μg/mL) [9, 10]. These studies also document an increasing trend in multidrug resistance among penicillin-resistant pneumococci.

Over the past several decades, many new antibacterial agents have been developed. Use of these agents in treating community-acquired respiratory tract infections has been largely empirical because isolating pathogens from patients remains uncommon and, in many cases, unreliable because of a lack of accurate diagnostic measures [11–14]. In most community-acquired respiratory tract infections, no microbiological testing is performed, nor are pathogens isolated [15]. Empirical treatments should include agents with activity against susceptible and resistant pneumococci because *S. pneumoniae* is one of the most common etiologic pathogens of community-acquired pneumonia [16]. The growing incidence of DRSP has become a major therapeutic concern as a number of formerly potent antipneumococcal agents have become increasingly less effective. The therapeutic effectiveness of various antibacterial classes in treating community-acquired respiratory infections due to DRSP is discussed below.

**Dosing Considerations in Antibacterial Resistance**

In local communities, the development of resistance may be due partly to selection effects associated with agents used for individual dosing of patients. The emergence of *S. pneumoniae* strains with low-level resistance can occur when either low concentrations of drugs or antibiotic agents that preferentially target low-level resistance are used [17–19]. In fact, it has been suggested that antimicrobial resistance patterns are most likely to appear in respiratory infections because of the inadequate dosing regimens for many of the oral antibiotics [20]. Higher concentrations of agents, which target high-level resistance and achieve complete bactericidal activity, may eradicate these resistant strains. However, an increased proportion of highly resistant strains, relative to the use of antibacterial agents, may result.

Given the selection effects that may be associated with either high or low doses, the pharmacokinetics (PK) and pharmacodynamics (PD) of an antibacterial agent play an integral role, and drug penetration at different infection sites must be considered. For *S. pneumoniae*, an extracellular bacterial pathogen,
Table 1. Activity of β-lactam agents against penicillin-susceptible (Pen\(^{-}\)), intermediately penicillin-resistant (Pen\(^{i}\)), and penicillin-resistant (Pen\(^{r}\)) pneumococci.

<table>
<thead>
<tr>
<th>Agent</th>
<th>MIC range, μg/mL</th>
</tr>
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<tbody>
<tr>
<td>Penicillin G(^{r})</td>
<td>0.015 - 0.06</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.015 - 0.06</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>0.015 - 0.06</td>
</tr>
<tr>
<td>Amoxicillin(^{r})</td>
<td>0.015 - 0.06</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate(^{r})</td>
<td>0.015 - 0.25</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.015 - 0.5</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>0.06 - 0.25</td>
</tr>
<tr>
<td>Cefuroxime(^{r})</td>
<td>0.03 - 2</td>
</tr>
<tr>
<td>Cefixime(^{r})</td>
<td>0.5 - 16</td>
</tr>
<tr>
<td>Cefaclor(^{r})</td>
<td>0.5 - 4</td>
</tr>
<tr>
<td>Cefprozil(^{r})</td>
<td>0.5 - 1</td>
</tr>
</tbody>
</table>

NOTE. Data are adapted from [22, 23].

\( ^{a}\) 1466 total isolates: 732 were Pen\(^{-}\) (MIC, <0.06 μg/mL), 254 were Pen\(^{i}\) (MIC, 0.12 - 1.0 μg/mL), and 480 were Pen\(^{r}\) (MIC, >2.0 μg/mL).

Penicillin Resistance and β-Lactam Therapy

Patterns of antimicrobial resistance are usually bimodal, with clear differences between low and high levels of resistance. In *S. pneumoniae*, however, β-lactam resistance is caused by incremental decreases in the affinity of penicillin-binding proteins, which give rise to a more continuous pattern of resistance [21]. In addition, many resistant pneumococci have defective auto-lysis that renders the organism tolerant to β-lactam antibiotics and other agents. Given the continuous pattern of resistance, the MIC of an antibacterial agent is a useful measure, together with other PK and PD criteria, of activity against *S. pneumoniae* [20]. The modal MIC reflects the concentration at which the largest percentages of isolates, which may have varying degrees of penicillin susceptibility, are inhibited by the specific agent. Measures of concentrations that inhibit 50% and 90% of isolates (MIC\(_{50}\) and MIC\(_{90}\), respectively) are also used.

The activity of several oral β-lactam agents against *S. pneumoniae* is documented in table 1. Although β-lactam agents exhibit strong activity against penicillin-susceptible *S. pneumoniae*, the potency tends to decrease as resistance to penicillin increases (table 1) [22, 24]. Penicillin G, ampicillin, and amoxicillin are all active against penicillin-susceptible *S. pneumoniae*, with MICs ranging from 0.015 to 0.12 μg/mL. Against non-penicillin-susceptible strains, amoxicillin is slightly more active, with an MIC that is ~1 dilution lower than that of either penicillin G or ampicillin. The activity of these agents is not improved by the addition of a β-lactamase inhibitor, such as sulbactam or clavulanic acid, because penicillin resistance in *S. pneumoniae* is not mediated by β-lactamase production.

Studies with animal models indicate that in order for β-lactam agents to be effective, the serum concentration must be greater than the MIC for at least 40% of the dosing interval for penicillins and at least 50% of the dosing interval for cephalosporins [25]. By using standard dosing regimens and the serum PK of the agent, these values can be employed as PK/PD breakpoints. Jacobs and colleagues [22] have demonstrated that susceptibility values for several older cephalosporins such as cefaclor and cefixime are low at PK/PD breakpoints. A comparison of several β-lactam agents shows that all oral cephalosporins provide a serum level above the MIC for penicillin-susceptible *S. pneumoniae* for at least 50% of the dosing interval [25, 26] (table 2). However, only parenteral β-lactam agents such as ceftriaxone maintain a time above the MIC (i.e., >90% of the dosing interval for strains of *S. pneumoniae* that are intermediately penicillin-resistant or penicillin-resistant). Of the oral β-lactam agents, only amoxicillin maintains a serum concentration above the MIC\(_{90}\) for at least 40% of the dosing interval for both intermediately penicillin-resistant and penicillin-resistant pneumococci. Cefuroxime, cefprozil, and perhaps cefpodoxime approach the required PK/PD criteria for intermediately penicillin-resistant pneumococci but not penicillin-resistant strains. Overall, it has been reported that of the available β-lactam antibiotics, only oral amoxicillin/clavulanate and intramuscular ceftriaxone demonstrate >90% activity against susceptible strains of *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [28].

These data suggest that, compared with the penicillins, most oral cephalosporins demonstrate less potent activity against *S. pneumoniae*, even against many penicillin-susceptible strains (table 1). Moreover, as penicillin resistance increases, there is a concomitant increase in the MICs of older-generation oral cephalosporins. Parenteral and more recent cephalosporin compounds have demonstrated good in vitro activity against penicillin-susceptible and penicillin-resistant strains of *S. pneumoniae*.

Table 2. Time above MIC (T > MIC\(_{90}\)) of β-lactam agents for *Streptococcus pneumoniae*.

<table>
<thead>
<tr>
<th>β-lactam agent</th>
<th>T &gt; MIC(_{90}), % of dosing interval</th>
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<tbody>
<tr>
<td>Amoxicillin, 23 mg/kg b.i.d.</td>
<td>100</td>
</tr>
<tr>
<td>Amoxicillin, 13 mg/kg b.i.d.</td>
<td>100</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>100</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>83</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>75</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>75</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>60</td>
</tr>
<tr>
<td>Cefixime</td>
<td>59</td>
</tr>
</tbody>
</table>

NOTE. Pen\(^{i}\), intermediately penicillin-resistant; Pen\(^{r}\), penicillin-resistant; Pen\(^{s}\), penicillin-susceptible. In this study, breakpoints (μg/mL) were used to define susceptibility as recommended by the National Committee for Clinical Laboratory Standards [27], with the exception of cefaclor and cefpodoxime, for which susceptibility is guided by the penicillin reaction. Data are from [20, 25, 26].
iat, especially strains for which MICs are between 0.12 and 1.0 g/mL [9, 29]. It is interesting that increasing resistance to ceftaxime and ceftriaxone in pneumococcal meningitis has been reported [30].

β-Lactam agents have also demonstrated poor in vitro activity against the most common atypical pathogens of community-acquired pneumonia, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species, which may account for up to 50% of cases in select populations [31]. Because the β-lactam agents are not active against the most common atypical pathogens, another agent, such as a macrolide, should be added to the treatment regimen if a β-lactam antibiotic is used and infection with an atypical pathogen is suspected. Recent guidelines for the empirical treatment of community-acquired pneumonia by the Infectious Diseases Society of America (IDSA) suggest that doxycycline, a macrolide, or fluoroquinolone as preferred therapy for community-acquired infections [32]. Combined treatment recommendations from the IDSA, the American Thoracic Society, and the Centers for Disease Control and Prevention are expected in early 2000 [33, 34]. Initial indications suggest that the recommendations for appropriate antibiotic coverage for suspected atypical pathogens will include doxycycline, a macrolide, or fluoroquinolone as preferred therapy.

Macrolide Resistance in *S. pneumoniae*

In the United States, macrolides are active against penicillin-susceptible strains of *S. pneumoniae*. Increased penicillin resistance, however, has been associated with macrolide resistance. In the United States, 1 study with 1466 isolates of *S. pneumoniae* found very little macrolide resistance (≤5%) in penicillin-susceptible strains [22]. However, 37% of intermediate penicillin-resistant strains (MIC, 0.12–1.0 g/mL) and 66% of penicillin-resistant strains (MIC, ≥2.0 g/mL) were also resistant to macrolides and azalides. These data are supported by another US surveillance study reporting that, although overall rates of resistance to macrolides in the United States in 1997 were 11.7%–14.3%, 64.5% of intermediate penicillin-resistant and penicillin-resistant *S. pneumoniae* strains were also resistant to erythromycin [9]. In France and Spain, even higher rates have been reported, with up to 80% of non-penicillin-susceptible *S. pneumoniae* isolates demonstrating macrolide resistance and resulting in failure of therapy for pneumonia [35, 36].

A somewhat anomalous situation exists in Italy, where a 48% incidence of macrolide resistance has been reported in the absence of penicillin resistance [37]. An *S. pneumoniae* clone that is multiliegend drug resistant but penicillin susceptible (serotype 6B) appeared in Italy, Spain, Greece, Israel, and other southern Mediterranean countries [38]. Macrolide resistance in Italy is not totally independent of penicillin resistance; 88% of non–penicillin-susceptible *S. pneumoniae* strains are resistant to macrolides [37]. Because of the high rate of cross-resistance between β-lactam agents and macrolides in *S. pneumoniae*, misuse of either β-lactam or macrolide antibiotics may result in the development of multidrug-resistant strains [37].

Two gene families, *erm* and *mef*, are currently known to be involved in the development of macrolide resistance, with inducible expression associated with the *erm* gene [39]. The expression of *erm* results in a high level of resistance to all macrolides, as well as to clindamycin. In southern Europe where the rate of macrolide resistance is high, this phenotype is found in ~80% of macrolide-resistant *S. pneumoniae* [40]. The expression of *mef* results in lower-level resistance to the 14- and 15-membered ring macrolides (erythromycin, clarithromycin, and azithromycin) but susceptibility to clindamycin and the 16-membered ring macrolides (spiramycin and josamycin). In the United States, both *erm* and *mef* play an important role in macrolide resistance among pneumococci [41].

For determining clinical efficacy of macrolides, investigators have proposed that the time the drug concentration in serum exceeds the MIC for >40% of the dosing interval may be the most effective PK/PD parameter [26]. For azalides, the area under the serum concentration versus time curve to MIC ratio appears to be most important for determining clinical efficacy. By using these PK/PD breakpoints for penicillin-susceptible isolates of *S. pneumoniae*, susceptibility values for clarithromycin and azithromycin have been found to be ≥94% [22]. The susceptibility data for both agents are greatly reduced with increasing *S. pneumoniae* resistance to penicillin, with ~65% susceptibility for intermediately penicillin-resistant isolates and ~33% susceptibility for penicillin-resistant strains [22]. Standard dosing regimens with both erythromycin and clarithromycin as treatment for patients with otitis media due to susceptible and resistant strains of *S. pneumoniae* have been found to produce serum concentrations during ≥88% of the dosing interval [20].

It has been proposed that an important factor in increased macrolide resistance may be the use of newer long-acting macrolides [37]. The long-acting agents are those with extended PK and dosing intervals, including spiramycin, roxithromycin, clarithromycin, and azithromycin. Short-acting macrolides, such as erythromycin, dirithromycin, and josamycin, have short half-lives and require more frequent dosing (3–4 times per day). An analysis of the correlation between overall macrolide use and resistance in community-acquired lower respiratory tract infections was conducted with the use of prescribing data from IMS Health (Plymouth Meeting, PA), resistance data from the Alexander Project, and previously reported resistance data [37]. Hospitalization was the only preexisting risk factor associated with antimicrobial resistance that was accounted for in the study. When plotted against the use of newer long-acting macrolides, a linear increase in macrolide resistance occurred with a correlation of 0.896 (r = 8.26; R² = 0.80; figure 1). No apparent correlation, however, occurred with the older short-acting macrolides. In the United States, an overall decrease in the volume of prescriptions for macrolides between 1992 and 1996
was observed; however, the number of prescriptions for the long-acting macrolides, clarithromycin and azithromycin, increased. This increase in the number of prescriptions was highly correlated with the increased incidence of resistance to both clarithromycin (r = 0.86) and azithromycin (r = 0.82) [37]. Although these relationships do not necessarily imply cause and effect, they do merit further investigation.

On the basis of published treatment guidelines from the IDSA, macrolides have been recommended as initial treatment for community-acquired infections. They appear to show good in vitro activity against the most common atypical respiratory pathogens [42]. However, PK/PD data suggest that of the currently available β-lactam and macrolide antibiotics, only amoxicillin/clavulanate and ceftriaxone are active against >90% of S. pneumoniae isolates [28]. The newer macrolides, clarithromycin and azithromycin, both demonstrate relatively good in vitro activity against key respiratory tract pathogens such as penicillin-susceptible S. pneumoniae (MIC90 ≤0.12 µg/mL) [22]. However, their activity against H. influenzae remains suspect; in 1 study, no isolates of H. influenzae are susceptible to either clarithromycin or azithromycin when previously defined PK/PD breakpoints are used [22]. In addition, the serum concentration of macrolides is actually much lower than their MIC90, which poses a clinical concern as both S. pneumoniae and H. influenzae are located extracellularly [43]. The concentration of some macrolides, such as clarithromycin in the epithelial lining fluid, may allow for higher achievable levels [41]; however, this hypothesis has not yet been proven. Therefore, the actual activity of macrolides and azalides against key respiratory pathogens located in extracellular tissue fluids, such as S. pneumoniae and H. influenzae, remains unclear.

Antipneumococcal Activity of Quinolones

Newer quinolones such as gatifloxacin (MIC90 ≤0.5 µg/mL), gemifloxacin (MIC90 ≤0.06 µg/mL), moxifloxacin (MIC90 ≤0.25 µg/mL), and sparfloxacin (MIC90 ≤0.5 µg/mL) have enhanced activity against S. pneumoniae [44–46]. Moreover, all of the quinolones maintain activity against non–penicillin-susceptible strains. The newer fluoroquinolones (gatifloxacin, gemifloxacin, moxifloxacin, and sparfloxacin) demonstrate fourfold to eightfold improved activity over ciprofloxacin and levofloxacin against S. pneumoniae [44–46]. In a time-kill study of the activity of quinolones against 4 isolates each of penicillin-susceptible, intermediately penicillin-resistant, and penicillin-resistant S. pneumoniae, gatifloxacin was bactericidal at twice the MIC90 [47] (table 3). The rate of killing for newer fluoroquinolones is relatively rapid. For example, with gatifloxacin, there is evidence of bactericidal activity occurring at ~6 h [44]. At ≤0.5 µg/mL, uniform bactericidal activity (99.9% killing) was observed within 24 h after exposure to the drug. By comparison, initiation of bactericidal activity with β-lactam agents occurs later, at ~12 h after exposure. Although macrolides are generally described as bacteriostatic rather than bactericidal, very slow killing does occur. At 2–4 times the MIC of a macrolide, bactericidal activity can be observed at ~24 h after exposure to the drug.

In addition to good bactericidal activity of quinolones against S. pneumoniae, the current incidence of quinolone resistance is low. In a recent study conducted by the SENTRY Antimicrobial Surveillance Program, the incidence of quinolone resistance in S. pneumoniae was <0.3% [48]. The incidence of quinolone resistance was also reported to be <1% in France, a country in which fluoroquinolones are used rather extensively [35]. Quinolone (ciprofloxacin and ofloxacin) resistance in S. pneumoniae has also been monitored by the Alexander Project.

<table>
<thead>
<tr>
<th>Agent</th>
<th>MIC90 µg/mL</th>
<th>MIC90 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pen&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Pen&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>0.5</td>
<td>0.25</td>
</tr>
</tbody>
</table>

NOTE: For gatifloxacin, ciprofloxacin, levofloxacin, and sparfloxacin, there were 81 Pen<sup>5</sup> isolates, 71 Pen<sup>1</sup> isolates, and 55 Pen<sup>8</sup> isolates; data are adapted from [44]. For moxifloxacin, there were 336 Pen<sup>5</sup> isolates, 108 Pen<sup>1</sup> isolates, and 56 Pen<sup>8</sup> isolates; data are adapted from [45].
from 1992 to 1996, no notable increases in the antipneumococcal activity of the compounds were observed, and no increasing trend of quinolone resistance in *S. pneumoniae* appears to be developing. A Canadian surveillance study of 7551 *S. pneumoniae* isolates has noted an increase in resistance to ciprofloxacin (MIC, $\geq 4 \mu g/mL$) from 0 in 1993 to 1.7% in 1997 and 1998 [49]. The MICs of the other quinolones in this study also increased over time; however, the newer fluoroquinolones generally had MICs that were at least 4 times lower than that of ciprofloxacin. The rates of resistance correlated with increased use of the quinolone agents and penicillin.

Pharmacodynamically, the use of fluoroquinolones has been correlated with reductions in the emergence of resistant pathogens when the peak concentration–to-MIC ratio is $>8.0$ [20]. In addition to activity against *S. pneumoniae*, quinolones provide good coverage for *H. influenzae*, *M. catarrhalis*, and the atypical respiratory tract pathogens [31]. The combined guidelines of the IDSA, American Thoracic Society, and Centers for Disease Control and Prevention are expected to recommend newer fluoroquinolones as empirical therapy for community-acquired respiratory infections especially when atypical pathogens are suspected [33, 34]. Quinolone treatment of children, however, has been limited mostly to use based on compassionate protocol.

**Conclusion**

Given the prevalence of *S. pneumoniae* as an etiologic pathogen of community-acquired respiratory tract infections, targeting of this organism is a major consideration in the choice of appropriate empirical therapy. Although β-lactam agents have good activity against penicillin-susceptible *S. pneumoniae*, their efficacy decreases as penicillin resistance increases. Amoxicillin, parenteral penicillin G, and the third-generation cephalosporins were identified by the IDSA guidelines as preferred agents only in the treatment of infections due to penicillin-susceptible and intermediately penicillin-resistant strains [32]. Moreover, as a class, β-lactam agents do not adequately cover atypical respiratory tract pathogens, thus limiting their use in the empirical treatment of community-acquired pneumonia if an atypical pathogen is suspected [31].

Macrolides can be effective in the treatment of pneumococcal infections; these agents alone or in combination with a β-lactam agent are considered appropriate for the empirical treatment of community-acquired pneumonia [32]. However, caution must be taken when using these agents empirically, since in vitro studies have found that they are often ineffective against non–penicillin-susceptible strains. In addition, macrolide activity against *H. influenzae* remains suspect. The IDSA guidelines do not recommend the use of macrolides against *S. pneumoniae* strains considered intermediately penicillin-resistant (MIC, 0.1–1 μg/mL) or those with high-level penicillin resistance (MIC, $\geq 2 \mu g/mL$) [32]. The newer quinolones (gatifloxacin, gemifloxacin, moxifloxacin, and sparfloxacin) have demonstrated good activity against both susceptible and nonsusceptible pneumococcal isolates. IDSA guidelines have recommended the fluoroquinolones as antimicrobials with activity against penicillin-susceptible strains of *S. pneumoniae* and as preferred agents with activity against intermediately penicillin-resistant strains and those with high-level penicillin resistance [32]. The additional activity of these agents against many aerobic and atypical pathogens identifies them as effective empirical treatments of community-acquired respiratory infections [31, 32]. Furthermore, the incidence of quinolone resistance among *S. pneumoniae* has to date remained low. The recent documentation in Canada of increasing resistance to older quinolones illustrates the importance of optimizing dosing regimens to preserve the efficacy of these agents.

Effective antimicrobial treatment of *S. pneumoniae* varies with the penicillin susceptibility of the infectious isolate. Therefore, the existence of resistant pneumococcal strains should be considered in the empirical treatment of community-acquired pneumonia. Careful selection of antimicrobials and their dosing schedules is necessary to decrease the spread of resistant strains of *S. pneumoniae*.

**References**


