Macrolides are currently recommended as first-line agents for the empirical treatment of community-acquired pneumonia. Heavy use of these agents for a variety of indications has resulted in an increasing incidence of macrolide resistance among pneumococcal isolates. Although several case reports and small case series have suggested that in vitro macrolide resistance is associated with treatment failure in cases of pneumococcal pneumonia, other observational data suggest that drug susceptibility testing may not correlate with treatment failure. In this article, we review current information on the mechanisms of macrolide resistance and the pharmacodynamics of macrolide therapy, together with efficacy data from animal models and clinical observations, to begin to gauge the clinical significance of macrolide resistance in *Streptococcus pneumoniae*. Areas for further investigation are highlighted.
with data from animal models and clinical observations in an attempt to gauge the clinical significance of macrolide resistance in *S. pneumoniae* and to identify areas for further investigation.

**MACROLIDE RESISTANCE IN S. PNEUMONIAE**

In vitro macrolide resistance in pneumococci is currently defined by erythromycin and clarithromycin MICs of >0.5 μg/mL and/or an azithromycin MIC of >1 μg/mL [18]. Resistance to macrolides occurs via 1 of the following 2 mechanisms: target-site modification or active drug efflux. Target-site modification is conferred by the *ermB* gene, which codes for a ribosomal methylase that methylates a single adenine residue on the 23S rRNA and markedly reduces the affinity of macrolides for their target site on the ribosome. This mechanism results in high-level macrolide resistance (i.e., MIC of erythromycin >64 μg/mL) and cross-resistance with lincosamides, such as clindamycin and streptogramin B drugs (so-called MLSB resistance), because of their overlapping binding sites on the ribosome. On the other hand, active drug efflux among pneumococci is mediated by a membrane efflux pump encoded by the *mefA* gene. This pump confers resistance to macrolides but not to clindamycin or streptogramins. This mechanism results in low-to-mid-level resistance, with MICs of erythromycin of 1–32 μg/mL.

It is interesting that the prevalence of the respective macrolide resistance mechanisms varies by geographic region [19]. The efflux mechanism accounts for more than two-thirds of resistant isolates in North America [20, 21]. In Europe and South Africa, however, ribosomal methylation is the predominant form of macrolide resistance [19]. Fortunately, most of the dramatic increase in macrolide resistance in the United States since 1993 is attributable to the efflux mechanism [20, 21]. These facts give rise to a second critical question: should all MRSP be considered equal, or does the mechanism of resistance determine whether in vitro macrolide resistance is clinically significant? Although this remains an open question with little supporting evidence from the clinical arena, there are pharmacodynamic data and results from experimental animal models that suggest that the clinical significance of MRSP is determined by the mechanism of resistance.

**PHARMACODYNAMIC APPROACH TO MACROLIDE RESISTANCE**

The science of pharmacodynamics describes the relationship between the in vitro potency of an antibiotic (e.g., the MIC) and the time course of its activity. The latter aspect is determined by the rate of bacterial killing, the effect of changing concentrations of the drug on this rate, and the presence of persistent effects on bacterial growth after the antibiotic is removed (i.e., postantibiotic effects). Specific pharmacodynamic parameters that correlate with antibacterial activity include the “time above MIC” (expressed as the proportion of the dosing interval during which plasma concentrations exceed the MIC), the maximal plasma concentration (*C* max) divided by the MIC (*C* max/MIC), and the area under the 24-h plasma concentration-time curve (AUC) divided by the MIC (AUC/MIC). For a given antibiotic class, specific pharmacodynamic parameters can be used to predict antimicrobial efficacy in animal models and, when investigated, in humans. These parameters can then be used to compare drugs within or between antibiotic classes, as well as different dosing regimens of the same drug, to determine their potential to eradicate both antibiotic-susceptible and -resistant bacterial populations [22]. The most important pharmacodynamic parameters for predicting macrolide activity are not conclusively established. As with β-lactams, the time above MIC appears to correlate best with efficacy for erythromycin and clarithromycin, and optimal efficacy is obtained when the time above MIC is >40%–50% of the dosing interval [22]. For azithromycin, it appears that the AUC/MIC is the most important parameter and that this ratio should be >25 for in vitro efficacy against pneumococcal infection [23].

The newer macrolides, clarithromycin and azithromycin, differ substantially in their pharmacokinetic profiles. For clarithromycin, a 500-mg oral dose produces a plasma *C* max of 2.5 μg/mL and an AUC of 19 μg-h/mL [24]. On the other hand, a 500-mg oral dose of azithromycin produces a *C* max of only 0.4 μg/mL and an AUC of 3.4 μg-h/mL after a 500-mg dose [24]. Therefore, the target AUC/MIC ratio for the optimal efficacy of azithromycin is obtainable in plasma only if the MIC for the infecting isolate is <0.25 μg/mL, which is notably less than the current resistance breakpoint of 2 μg/mL. Thus, the plasma concentrations of the macrolides alone do not support their use for infections caused by MRSP.

More important than plasma concentrations, however, are the drug concentrations at the site of infection. By virtue of exceptional tissue penetration and long tissue-elimination half-lives, newer macrolides may achieve concentrations in the lung that are substantially greater than plasma concentrations. In the case of pneumonia caused by extracellular pathogens such as *S. pneumoniae*, antimicrobial concentrations in the alveolar epithelial lining fluid (ELF) (and, to a lesser extent, within leukocytes and alveolar macrophages) are likely more important for determining therapeutic efficacy than are plasma concentrations. Mean steady-state concentrations of both clarithromycin and azithromycin in the ELF of normal volunteers are significantly higher than those in plasma (table 1) [25, 26]. After repeated doses, mean clarithromycin concentrations are >32 μg/mL in the ELF and >10-fold higher than this inside alveolar macrophages 4 h after dosing. Twelve hours after dosing, drug concentrations in ELF and alveolar macrophages
are generally still >16 μg/mL. Azithromycin does not concentrate as well in the ELF, where achievable concentrations are ~1 μg/mL in normal volunteers, but it is heavily concentrated intracellularly. In addition, a variety of studies suggest that azithromycin concentrations are higher in the presence of inflammation, where drug is delivered to the site of infection by leukocytes [27]. If this is the case, pharmacokinetic studies involving healthy volunteers are unlikely to fully reflect the intrapulmonary drug concentrations in patients with pneumonia. Similarly designed pharmacokinetic studies should be performed in patients with CAP who are undergoing bronchoscopy for a clinical indication. Such studies should include, not only patients receiving macrolide-containing regimens at the time of bronchoscopy, but also patients who are receiving nonmacrolide antibiotics. To avoid biasing samples toward failure of a macrolide-containing regimen, patients in the latter group could receive a macrolide in addition to their nonmacrolide regimen before the procedure.

**IMPACT OF MACROLIDE RESISTANCE**

The preceding pharmacodynamic argument suggests that pneumonia caused by *S. pneumoniae* with lower levels of macrolide resistance (MICs, ≤16 μg/mL) may be effectively treated with clarithromycin and, possibly, azithromycin. Unfortunately, the existing clinical data are inadequate to determine whether in vitro macrolide resistance predicts adverse treatment outcomes, and properly controlled prospective human trials are unlikely to be performed. In the absence of clinical data, experimental animal models may provide useful information. Hoffman et al. [28] evaluated the efficacy of clarithromycin and azithromycin against 19 pneumococcal strains with widely varying susceptibilities to macrolides in a leukopenic mouse model of pneumococcal pneumonia. Drug dosages were selected to mimic the serum pharmacokinetics observed in humans receiving standard dosages. Among animals infected with 1 of 9 *ermB*-producing isolates (clarithromycin MICs of 0.5–16 μg/mL and azithromycin MICs of 1–32 μg/mL), treatment with clarithromycin significantly improved survival rates among mice infected with any of the 9 isolates, whereas treatment with azithromycin improved survival only for those infected with either of 2 of the 9 isolates, each with an azithromycin MIC of 2 μg/mL. Neither drug improved survival among mice infected with any of the 5 *ermB*-producing isolates (MICs, >64 μg/mL). Using a similar model, Tessier et al. [29] demonstrated significant reductions in lung colony forming units for infections caused by isolates with MICs as high as 4 μg/mL (but not 8 μg/mL) when treated with similar doses of clarithromycin; however, survival was not improved for mice infected with isolates with MICs of ≥4 μg/mL.

Two caveats should be considered when interpreting the results of these 2 studies. First, the use of leukopenic mice may negatively influence the results, because the macrolides (in particular, azithromycin) may be carried to the source of infection within leukocytes. Second, mice infected via intratracheal instillation are generally bacteremic within 24–72 h. In this context, it is likely that treatment outcomes were determined by serum, rather than intrapulmonary, drug concentrations. Therefore, models involving intratracheal or intranasal instillation may better represent bacteremic pneumococcal pneumonia, rather than the nonbacteremic disease that comprises the majority of both inpatient and outpatient pneumonias. A nonbacteremic animal model of pneumonia would provide a better tool for studying the impact of intrapulmonary drug concentrations.

The clinical data available with regard to the impact of macrolide resistance on treatment outcomes have been limited to anecdotal case reports and case series, with the exception of a single large observational study. The preceding pharmacodynamic argument predicts that macrolides would have limited efficacy for treating bacteremic pneumonia caused by resistant *S. pneumoniae*, the outcomes of which are more dependent on serum drug concentrations. Indeed, a multitude of case reports and small case series have recently described breakthrough bacteremia with resistant isolates during or immediately following macrolide therapy [9–12, 14, 15]. To date, these clinical failures have generally occurred in outpatients receiving oral macrolide therapy for infection caused by isolates with MICs ≥8 μg/mL, although failures of parenteral macrolide therapy have also been reported [10, 11], and, in 1 case, the erythromycin MIC was <4 μg/mL [14]. Erythromycin, azithromycin, and clarithromycin have each been represented among the clinical

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**Table 1. Mean steady-state concentrations of 2 newer macrolides, clarithromycin and azithromycin, in plasma and lung after completion of an oral dosage regimen.**

<table>
<thead>
<tr>
<th>Time of measurement</th>
<th>Mean concentration by sample type, μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
</tr>
<tr>
<td>4 h after dosage</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>2.0–3.3</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.08–0.09</td>
</tr>
<tr>
<td>At trough concentration</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.9–1.2</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.03–0.05</td>
</tr>
</tbody>
</table>

**NOTE.** Clarithromycin concentrations were measured after administration of 9 doses of 500 mg po q12h. Azithromycin concentrations were measured after administration of 1 dose of 500 mg and 4 subsequent doses of 250 mg po q24h. Data are from [25, 26].

a For clarithromycin, 12 h after dosage, and for azithromycin, 24 h after dosage.
failures. The most compelling cases for clinical failure due to macrolide resistance are those in which bacteremia persists after >48 h of macrolide therapy and therapeutic success follows a switch to another antimicrobial class. For example, Waterer et al. [10] reported a previously healthy 49-year-old woman admitted to the hospital with bilobar pneumonia, but with a low score on the Pneumonia Severity Index, who developed septic shock after >72 h of intravenous azithromycin therapy and died from pneumococcal bacteremia. The bloodstream isolate had an erythromycin MIC of 16 μg/mL.

In a recent case series, Lonks et al. [14] identified 86 patients with pneumococcal bacteremia due to macrolide-nonsusceptible S. pneumoniae (MNSP; erythromycin MIC, ≥0.5 μg/mL) over a 13-year period at 4 study centers. In a matched case-control analysis involving patients with bacteremia due to MSSP as control subjects, Lonks et al. [14] found that concurrent macrolide therapy at the time of blood culture was a risk factor for bacteremia due to MNSP. This does not clearly establish, however, that all patients with MNSP are less likely to respond to macrolide therapy than are those with MSSP. In fact, it is remarkable that only 19 cases of breakthrough bacteremia in patients receiving macrolides were identified over such a lengthy period at 4 academic medical centers. Moreover, in only 1 case of breakthrough bacteremia during macrolide therapy was the erythromycin MIC for the MNSP isolate <16 μg/mL. In that case, the patient—from whom an isolate with a macrolide MIC of 4 μg/mL was recovered—did not respond to therapy that included erythromycin and azithromycin. Therefore, in the context of the pharmacodynamic argument presented above, no legitimate conclusions can be drawn from clinical data on the risk of macrolide failure due to efflux-mediated resistance mechanisms, particularly if the MIC for the infecting strain is <16 μg/mL.

Another recently published case series also fails to gauge the clinical significance of efflux-mediated resistance. Van Kerkhoven et al. [15] reviewed all adult cases of pneumococcal bacteremia at a university hospital in Belgium and identified 12 cases of breakthrough bacteremia among patients who received a macrolide (clarithromycin; 4 cases) or a β-lactam (amoxicillin-clavulanate, 5 cases; cefadroxil, 2 cases; and cefaclor, 1 case) at the time of admission. It is notable that all 4 patients who received a macrolide had MRSP bloodstream isolates with erythromycin MICs of ≥256 μg/mL, whereas the 6 patients who did not respond to amoxicillin-clavulanate or cefaclor treatment had bloodstream isolates fully susceptible to penicillin (MICs, <0.016 μg/mL).

Thus, a careful review of these 2 recent case series reveals several important points. First, although evidence is mounting that high-level, ermB-mediated macrolide resistance is associated with occasional treatment failure, the true risk of treatment failure among all patients with high-level macrolide resistance remains unknown. Second, the risk of macrolide treatment failure as a result of low-level resistance (MICs, ≤16 μg/mL) mediated by drug efflux mechanisms remains unsubstantiated. Third, treatment failures regularly occur in infections caused by drug-susceptible or drug resistant isolates, and, given the increasing prevalence of infection with drug-resistant S. pneumoniae, more cases of treatment failure due to resistant isolates should be expected, without necessarily leading to conclusions that treatment failure was determined by the resistance trait. Although there is a large number of patients who develop pneumonia and receive treatment with macrolides, wholesale clinical failures are not occurring, despite the current levels of macrolide resistance.

A final caveat to these 2 recent case series reminds us that there is also more to gauging the clinical impact of resistance than assessing the risk of breakthrough bacteremia. Of the 23 cases of treatment failure with MRSP isolates identified in the 2 latter case series, only 1 infection (4% of cases) resulted in death [14, 15], giving a mortality rate significantly lower than the expected mortality rate of at least 12% among patients with bacteremic pneumococcal pneumonia [30, 31]. Moreover, the single death occurred in a 95-year-old patient for whom, on the basis of North American guidelines [1–3], initial inpatient, rather than outpatient, therapy would have been warranted. In the only prospective study in which outcomes for pneumococcal pneumonia were analyzed on the basis of macrolide susceptibility, Ewig et al. [16] were unable to demonstrate significantly increased mortality associated with MNSP (7%) versus MSSP (14%) infection, nor with discordant (12%) versus concordant (10%) therapy for treating MNSP infection. In fact, mortality was higher among those with MSSP infections, although the number of patients studied was small, and the differences were not statistically significant.

CONCLUSIONS

It seems probable that the mechanism of macrolide resistance will determine the degree of resistance and, therefore, the clinical impact of MRSP on pneumonia-related outcomes. Macrolide MICs associated with ermB-mediated resistance are ≥64 μg/mL—far greater than the macrolide concentrations routinely achieved in serum or in the ELF. As a result, the resistance conferred by this mechanism would be expected to be clinically relevant. For a majority of isolates with mefA-mediated resistance, however, the MICs are within a range of drug concentrations achievable in the ELF by routine dosing with clarithromycin or, possibly, azithromycin. As a result, current in vitro susceptibility breakpoints may underestimate the activity of these 2 macrolides against pneumococci with low-level drug resistance due to active drug efflux. The treatment of uncomplicated pneumonia caused by isolates with MICs as high as 8–16 μg/mL may be possible, because of the exceptional tissue penetration of the
MRSP infection is suspected or demonstrated. The clinical efficacy of all macrolides will vary. Fluoroquinolone is recommended in these settings. Large-scale observational studies in which the clinical failure rate among patients receiving macrolide therapy is assessed in association with macrolide breakpoints for pneumococcal pneumonia analogous to those recently established for some β-lactams. Large-scale observational studies in which the clinical failure rate among patients receiving macrolide therapy is assessed in association with the degree of macrolide resistance and with the failure rate among patients receiving nonmacrolide regimens are probably the most feasible studies to perform.

For now, macrolide monotherapy remains a reasonable alternative for outpatients and for the least severely affected inpatients without risk factors for drug resistance, as suggested by recent guidelines. For bacteremic disease or for more severe infection requiring hospitalization, however, caution is warranted when MRSP infection is suspected or demonstrated. Combination therapy with a β-lactam plus a macrolide or a respiratory fluoroquinolone is recommended in these scenarios. Continued monitoring of the clinical efficacy of all macrolides will be important as the prevalence and the magnitude of macrolide resistance continue to increase.

References