Clinical Relevance of Macrolide-Resistant
Streptococcus pneumoniae for Community-Acquired Pneumonia

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Macrolides are often the first choice for empirical treatment of community-acquired pneumonia. However, macrolide resistance among Streptococcus pneumoniae has escalated at alarming rates in North America and worldwide. Macrolide resistance among pneumococci is primarily due to genetic mutations affecting the ribosomal target site (ermAM) or active drug efflux (mefE). Prior antibiotic exposure is the major risk factor for amplification and perpetuation of resistance. Clonal spread facilitates dissemination of drug-resistant strains. Data assessing the impact of macrolide resistance on clinical outcomes are sparse. Many experts believe that the clinical impact is limited. Ribosomal mutations confer high-grade resistance, whereas efflux mutations can likely be overridden in vivo. Favorable pharmacokinetics and pharmacodynamics, high concentrations at sites of infections, and additional properties of macrolides may enhance their efficacy. In this article, we discuss the prevalence of macrolide resistance among S. pneumoniae, risk factors and mechanisms responsible for resistance, therapeutic strategies, and implications for the future.

Streptococcus pneumoniae is the most common cause of community-acquired pneumonia (CAP), is implicated in 9%–55% of patients requiring hospitalization [1–3], and is the most common cause of death due to CAP [4, 5]. "Atypical" pathogens (e.g. Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella species) have been implicated in 8%–48% of cases of CAP; marked demographic, seasonal, and geographical variations exist [4–9]. Given their excellent activity against S. pneumoniae as well as atypical organisms, macrolide antibiotics (either alone or combined with β-lactams) have been widely used to treat CAP (including pneumococcal pneumonia) [1, 10–12]. In 1993, expert Consensus Statements from the American [11, 13] and Canadian [11, 13] Thoracic Societies recommended macrolides as drugs of choice for empiric treatment of CAP in low-risk patients. For patients requiring hospitalization (but not requiring intensive care), a β-lactam (with or without a macrolide) was advocated [11, 13]. In 1998, guidelines published by the Infectious Disease Society of America (IDSA) [14] advocated pathogen-directed therapy where appropriate. Macrolide antibiotics remained a viable first choice for empirical treatment of CAP in outpatients who could walk [14]. For patients requiring hospitalization, a parenteral β-lactam (with or without a macrolide) was advocated [14].

Within the past few years, the rapid escalation of resistance to multiple antibiotics among S. pneumoniae has cast doubt on the efficacy of macrolide antibiotics for serious pneumococcal infections [1]. In addition, there is a paucity of data regarding the use of macrolides for bacteremic pneumococcal pneumonias. Macrolides penetrate poorly into the CSF, making macrolides poor choices for suspected meningeval infections [1]. In light of these uncertainties, previous recommendations for treating CAP [11, 13, 14] were slightly modified. Revised guidelines (published in August 2000) from the...
IDSA [15] and a joint committee of the Canadian Infectious Disease Society and Canadian Thoracic Society [1] continued to advocate macrolide antibiotics (alone or combined with β-lactams) for empirical treatment of CAP. As per previous guidelines [11, 13, 14], recommendations for treatment were stratified on the basis of host, demographic, and pathogen-specific factors. In the most recent IDSA [15] and Canadian [1] guidelines, newer "respiratory" fluoroquinolones (FQs; e.g., levofloxacin, gatifloxacin, moxifloxacin) were incorporated into the treatment options because of their enhanced activity against S. pneumoniae (including penicillin- or macrolide-resistant strains). Both guidelines advocate either a macrolide, respiratory FQ, or doxycycline (no preference given) for empirical treatment of CAP in patients who lack significant comorbidities and who do not require hospitalization [1, 15]. For patients requiring hospitalization (but not care in an intensive care unit [ICU]), recommended therapeutic options were either a β-lactam plus a macrolide or a respiratory FQ alone [1, 15]. In the Canadian guidelines [1], respiratory FQs were advocated as preferred therapy for patients with chronic obstructive pulmonary disease who had received antibiotics or orally administered steroids within 3 months. The increasing role of FQ antibiotics in these new guidelines reflects concern about the marked escalation of penicillin and macrolide resistance among S. pneumoniae. FQs are attractive options for treating CAP because of their broad-spectrum activity against both typical and atypical pathogens, but overzealous use of FQs might lead to resistance to this class of antimicrobials [16–18].

Are the current rates of antibiotic resistance in the United States sufficient to justify reduction in the use of macrolide antibiotics? Some experts argue that the clinical importance of in vitro antimicrobial resistance among S. pneumoniae is greatly exaggerated [19, 20]. A recent report from the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group (DRSPTWG) suggested that in vitro susceptibility breakpoints for penicillin for S. pneumoniae were inappropriate for nonmeningeal infections and should be revised upward [20]. Further, the DRSPTWG argued that orally administered macrolides, doxycycline, or β-lactam antibiotics with good antipneumococcal activity should remain as preferred initial empirical therapy for CAP. They advised restricting newer FQs to patients whose infections fail to respond to therapy; to patients who are allergic to β-lactam or macrolide antibiotics; or for pneumococcal isolates displaying high-grade resistance to penicillin (e.g., MIC ≥4 µg/mL) [20]. They reasoned that overuse of FQs should be avoided in order to reduce the likelihood of emergence of antimicrobial resistance to this class of antibiotics. The authors admitted that macrolide resistance, when present, could adversely affect outcomes. Existing studies are inadequate to assess the role or limitations of macrolide antibiotics for community-acquired respiratory infections. How pervasive and important is macrolide resistance in the United States and globally today? Does in vitro resistance translate into clinical failures? Should changing resistance patterns modify our choice of therapy for CAP or for suspected pneumococcal pneumonia?

**IMPACT OF ANTIMICROBIAL RESISTANCE ON CLINICAL OUTCOMES**

Since the early 1990s, in vitro resistance of S. pneumoniae to β-lactams and macrolide antibiotics has escalated dramatically in North America [21–25]. However, data specifically evaluating the impact of macrolide resistance on clinical outcomes are sparse. More data are available regarding penicillin resistance among pneumococci, but the clinical importance remains controversial. Treatment failures may occur for a variety of reasons apart from antimicrobial resistance. Host factors (e.g., age, comorbidities) [26, 27] and virulence factors intrinsic to the organism [28] independently influence mortality, irrespective of antimicrobial susceptibility profiles. Although treatment failures due to penicillin or cephalosporin resistance have been reported with meningitis [29, 30] and otitis media [31–34], the relation between drug resistance and failure for the infection to respond to treatment in patients with pneumococcal pneumonia is not clear [26, 27, 35, 36]. Several studies of pneumococcal bacteremias cited similar mortality rates among patients with penicillin-resistant and penicillin-susceptible strains when other risk factors (e.g., age, comorbidities) were taken into account [26, 27, 35]. In a multicenter international study, fatality rates were higher in certain countries, likely related to specific clones of pathogens, but fatality rates did not correlate with antimicrobial nonsusceptibility [28]. Certain serotypes (e.g., serotype 3) were associated with increased mortality, even when isolates were fully susceptible to penicillin [28].

A prospective study in 5 countries of 460 episodes of pneumococcal bacteremia identified the following risk factors for death by multivariate analysis: age >65 years; living in a nursing home; presence of chronic pulmonary disease; high acute physiology (APACHE) scores; and need for mechanical ventilation [37]. Neither the particular antibiotic regimen nor frequency of antibiotic changes influenced prognosis [37]. Although these studies [28, 37] did not directly assess the impact of antimicrobial resistance on controlling pneumococcal infections, they underscore the importance of nonantibiotic factors influencing the course of invasive pneumococcal infections. However, recent articles cited higher mortality rates [38] or suppurative complications [39] for patients with bacteremic pneumococcal pneumonias when isolates displayed high level resistance to cefotaxime (MIC ≥2 [38]) or penicillin (MIC ≥4 µg/mL [38] or ≥2 µg/mL [39]) (macrolide resistance was not assessed). Resistance to FQs, albeit rare, has recently been described; many
such strains are also resistant to β-lactams and macrolides [16–18, 23, 40]. Although treatment failures have been cited with FQs [17], the frequency of this event appears to be rare. Here, we will limit our discussion to evolution of macrolide resistance among S. pneumoniae, genetic mechanisms, regional and global trends, and implications for therapy.

### DEFINITION OF MACROLIDE RESISTANCE

In 1996, in vitro breakpoints for erythromycin for S. pneumoniae as per the National Committee for Clinical Laboratory Standards were changed from >1 to <4 μg/mL (intermediate) and ≥4 μg/mL (resistant) to 0.5 μg/mL (intermediate) and ≥1 μg/mL (resistant) [41]. For S. pneumoniae, in vitro resistance to clarithromycin is defined by MIC >1 μg/mL; for azithromycin, the breakpoint is 2 μg/mL [42].

### MECHANISMS OF MACROLIDE RESISTANCE IN S. PNEUMONIAE

Resistance to macrolides occurs primarily through 2 mechanisms: target site (ribosomal) modification (MLSb phenotype) or active drug efflux (M phenotype) [43–46] (table 1). Pneumococci resistant to erythromycin (by either mechanism) are also resistant to azithromycin, clarithromycin, and roxithromycin [47–51]. Importantly, ribosomal modification results in resistance to macrolides, lincosamides (e.g., clindamycin) and streptogramins (MLSb phenotype), whereas efflux mutants affect only macrolides (M phenotype) [44, 45].

### MODIFICATION (MUTATIONS) AT THE RIBOSOMAL TARGET SITE

Macrolides and ketolides inhibit protein synthesis by binding to ribosomal target sites in bacteria, causing premature disassociation of the peptidyl-tRNA from the 50S ribosome [44, 49, 52, 53]. Macrolides also inhibit the assembly of new large ribosomal subunits, resulting in depletion of functional ribosomes within the cell [54]. The 16-member macrolides (e.g., miocamycin, spiramycin, rokitamycin, josamycin) bind to the same 50S subunits as 14- and 15-member macrolides but inhibit peptide bond synthesis more directly [44].

The binding site for macrolides and ketolides is situated within a deep cleft at the interface between the L4 protein of the large 50S ribosomal subunit and the underlying ribosomal RNA scaffold [55]. The structure of the drug-binding pocket within the 50S ribosomal unit is defined by the tertiary configuration of the 23S rRNA [44]. A peptidyl transferase in the V domain of 23S rRNA [46, 53] and hairpin 35 in domain II are important components—but not the sole components—of the binding site [44, 46, 56]. Nucleotide 2023 within the loop of 23S rRNA hairpin 72 is also implicated [44]. Mutations at any of these sites may perturb the tertiary structure of target sites, conferring resistance to macrolides and related antibiotics [44]. Several distinct mutations and phenotypes have been detected in laboratory and clinical settings [44, 55, 57]. The dominant mechanism, encoded by the *erm*AM (erythromycin ribosome methylation) gene, methylates a highly conserved region (A2058) of the peptidyl transferase loop in domain V of 23S mRNA [44, 45, 58].

The result of this RNA methylation is a conformational change in the ribosome that reduces the affinity of MLS antibiotics for the binding site [46]. Importantly, macrolide resistance conferred by *erm*AM is typically high grade (i.e., erythromycin MIC >64 μg/mL) [22, 59–61], whereas efflux mutations (discussed later) result in much lower erythromycin MICs (1–32 μg/mL) [45, 58, 59, 62].

The *erm*AM gene is not unique to pneumococcus and is found in other *Streptococcus, Staphylococcus, enterococci, and Escherichia coli* [46]. *erm*AM was first described in *Streptococcus*.

### Table 1. Mechanisms for macrolide resistance in *Streptococcus pneumoniae*.

<table>
<thead>
<tr>
<th>Mechanism and description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target site (ribosomal) modification: MLSb phenotype</strong></td>
</tr>
<tr>
<td>Erythromycin ribosome methylation (<em>erm</em>) gene</td>
</tr>
<tr>
<td>Predominant mechanism in Europe and South Africa</td>
</tr>
<tr>
<td>Can be carried on chromosomes, plasmids, or conjugative transposons</td>
</tr>
<tr>
<td>Confers high-grade resistance to erythromycin (MIC &gt;64 μg/mL)</td>
</tr>
<tr>
<td>Confers cross-resistance to macrolides, lincosamides, and streptogramins</td>
</tr>
<tr>
<td><strong>Efflux pump modification: M phenotype</strong></td>
</tr>
<tr>
<td>Macrolide efflux (<em>mefE</em>) gene</td>
</tr>
<tr>
<td>Predominant mechanism in North America</td>
</tr>
<tr>
<td>Chromosomal; can be transferred by conjugation</td>
</tr>
<tr>
<td>Intermediate levels of resistance to erythromycin (MIC 1–32 μg/mL)</td>
</tr>
<tr>
<td>Does not affect 16-member macrolides (e.g., josamycin), lincosamides or streptogramins</td>
</tr>
<tr>
<td>Additional mutations (non-<em>erm</em>AB, non-<em>mefE</em>)</td>
</tr>
</tbody>
</table>

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Macrolide-Resistant S. pneumoniae for CAP • CID 2002:34 (Suppl 1) • S29
sanguis, where it is carried on a plasmid pAM77 [46, 63]. Several dozen erm methyltransferase genes exist [53] and a new nomenclature system for different erm genes has been proposed [64]. These erm genes can be carried on chromosomes, plasmids, or conjugative transposons [53, 65]; expression of erm genes can be constitutive or inducible [50, 53, 66]. In pneumococci, ermB encodes a protein of 245 amino acids, which shares >98% homology with erm genes from S. sanguis, Enterococcus faecalis, E. coli, and Streptococcus pyogenes [45, 46, 58, 65, 67, 68]. In pneumococci, ermB is usually carried on conjugative transposons, Tn1545 [69] or Tn917 [46], which may facilitate rapid dissemination of erythromycin resistance [70]. Macrolide resistance in Europe [55, 59, 71–74] and South Africa [75] is predominantly mediated by ermB; efflux is infrequent. Recently, a clone of erythromycin-resistant pneumococci encoded by ermB was described in Greece [76]. Nucleotide sequences were identical to the ermB gene from a clinical strain of S. pyogenes [65].

In addition to ermAM, other mutations in ribosomal proteins or nucleotides may affect the binding site. Mutations in L4 or L22 ribosomal proteins perturb the conformation of residues in domains II, III, and V and inhibit antibiotic binding at domain V [55, 66, 77]. Mutations affecting the target site (whether by change in 23S rRNA or ribosomal proteins) results in a MLSB phenotype [51, 55, 61, 78] but do not affect ketolides [43, 66]. Rarely, ribosomal mutations confer resistance to lincosamides, but paradoxically, they increase susceptibility to erythromycin [79].

ALTERNATIONS IN PROTON PUMP (EFFLUX)

The second major mechanism of macrolide resistance is active (proton-dependent) efflux (the M resistance phenotype), which is encoded by the mefE (macrolide efflux) gene [45]. The mef genes (mefA in S. pyogenes and mefE in S. pneumoniae) are chromosomal [80] and can be transferred by conjugation [68]. First described in 1996, mefE confers resistance to 14- and 15-member macrolides but does not affect lincosamides, streptogramins, or 16-member macrolides [45, 80, 81]. Typically, pneumococci containing mefE have MICs to erythromycin of 1–32 μg/mL [45, 58, 59, 62]. The prevalence of ermB and mefE mechanisms varies according to geographic region. Efflux (mefE) accounts for 61%–85% of macrolide resistance in North America [22, 58, 78, 81, 82] and Japan [61] but accounts for <20% of macrolide-resistant pneumococcal isolates in Europe [55, 59, 71–74, 76] and South Africa [75]. Some macrolide-resistant pneumococci contain both mefE and ermB genes [61, 74, 78].

NOVEL MECHANISMS

In addition to erm and mef mutants, 1%–3% of macrolide resistant pneumococci lack mefE or ermB genes, indicating that additional mechanisms are operative [22, 55, 58, 78, 81]. Novel phenotypes and mechanisms of macrolide resistance were recently described in North America and Eastern Europe [55, 83]. Some mutants were highly resistant to macrolides, penicillins, and streptogramin B but remained susceptible to lincosycin and telithromycin [55]. Fortunately, most (>99%) of macrolide-resistant strains of S. pneumoniae remain susceptible to ketolides (novel agents within the macrolide class) [22, 53, 84, 85] and oxazolidinones (e.g., linezolid) [86, 87]. Vancomycin is uniformly (100%) active [22, 53, 83, 84, 88]. Recently, isolates of S. pneumoniae displaying only moderate resistance to macrolides but high-grade resistant to telithromycin (a ketolide) were described [55]. Other mutations at L4 conferred resistance to macrolides and streptogramins [55] and to ketolides [83]. Unusual resistance phenotypes have also been described. In France, isolates of S. pneumoniae exhibited resistance to 16-member macrolides and streptogramins but remained susceptible to 14- and 15-member macrolides, ketolides, and the lincosamides [83, 89].

IMPLICATIONS OF DIVERSE MECHANISMS OF RESISTANCE

Worldwide, ermB and mefE account for >97% of macrolide resistance among pneumococci, but the prevalence of these genes varies considerably among countries or regions. As has been discussed, erythromycin MICs range 1–32 μg/mL among pneumococci containing mefE [45, 58, 59, 62], whereas among ermB mutants, MICs typically exceed 128 μg/mL. Some strains with multiple ribosomal mutations exhibit >2000-fold increases in MICs compared with wild-type strains [55]. The MIC differences between ermAM and mefE mutants are likely to be important in vivo. Clinical failures can be expected with ermB strains, and concentrations of macrolides achieved in tissue or at sites of infections may override mefE mechanisms. Because efflux (mefE) accounts for >70% of macrolide resistance in North America [22, 58, 78, 81, 82, 90], overall rates of clinically significant macrolide resistance may approximate 4%–6% in the United States rather than 16%–22% [22, 78, 90].

GLOBAL TRENDS

Macrolide resistance among strains of S. pneumoniae has escalated dramatically within the past decade worldwide [21, 22, 90, 91], but prevalence rates are highly variable among countries (<3% to >70%) [49, 59, 71, 82, 90, 92–95]. Previous antibiotic exposure is a major risk factor for amplification and perpet-
ulation of resistance [59, 73, 92, 94, 96–98]. Antimicrobial resistance rates are higher in pediatric populations [24, 72, 78, 93, 99–104], in day care centers [73, 78, 105] or hospitals [100, 106–108], and among isolates from the middle ear, nasopharynx, or respiratory tract [24, 107]. Transmission of pneumococci from young children harboring \textit{S. pneumoniae} in the nasopharynx is a critical mechanism whereby drug-resistant clones are disseminated into the community (both to children and adults) [105, 109, 110]. The incidence of macrolide resistance is higher among penicillin-resistant strains [21, 22, 90, 91, 111], but macrolide resistance is also increasing independently of penicillin resistance [94, 111, 112].

Local, regional, and international surveillance studies have shown marked regional variability in rates of macrolide resistance. The Alexander Project, an international surveillance program established in 1992, tracks resistance rates from multiple laboratories and hospitals in North and South America, Europe, Asia, South Africa, Saudi Arabia, and Mexico [111]. During 1992–1996, macrolide resistance among pneumococci increased globally among both penicillin-susceptible and penicillin-resistant strains [111]. During 1996, 16.5% of all isolates were macrolide resistant [111]. Importantly, in 12 (63%) of 19 centers, macrolide resistance rates exceeded penicillin resistance rates. Among 10 centers in Europe, 23% of pneumococci isolated in 1995 exhibited macrolide resistance in vitro, but the variation among centers was great (0%–48%) [111]. Among 5 centers in the United States, macrolide resistance increased from 2.2% in 1993 to 13.9% in 1996. Rates of macrolide resistance at other sites were highly variable (i.e., Hong Kong, 68.2%; Mexico City, 31.4%; Saudi Arabia, 3.7%; Brazil, 3.2%) [111].

In a separate study, surveillance of respiratory tract isolates of \textit{S. pneumoniae} from 10 European countries in 1994–1995 cited erythromycin resistance rates ranging 0%–35% [113]. The highest rates of erythromycin resistance (>15%) were observed in Spain, Hungary, and France [113]. Typically, once antibiotic resistance clones are introduced into a region or country, levels of antimicrobial resistance increase over time (table 2). For example, in one hospital in Barcelona, Spain, the incidence of erythromycin resistance among \textit{S. pneumoniae} rose from 0 in 1979 to 9.4% in 1990 [114]. In a large national survey in Spain, erythromycin resistance increased from 10% in 1989 to 34% in 1997 [71]. Similarly, in Italy, erythromycin resistance among pneumococci rose from 6% in 1993 [117] to 23% in 1996 [115]. In another survey from central Italy, erythromycin resistance increased from 7% in 1993 to 33% in 1997 among community isolates of \textit{S. pneumoniae} [59]. Surveys in central Italy of nasopharyngeal isolates from young children cited macrolide resistance rates of 60%–64% [110, 118]. In Belgium, macrolide resistance increased from 1% in 1983 to 6.7% in 1987 [116].

Table 2. Rapid escalation of macrolide resistance in \textit{Streptococcus pneumoniae} worldwide in selected countries.

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>%</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barcelona, Spain</td>
<td>1979</td>
<td>9.4</td>
<td>1990</td>
</tr>
<tr>
<td>Spain</td>
<td>1989</td>
<td>34</td>
<td>1997</td>
</tr>
<tr>
<td>Italy</td>
<td>1993</td>
<td>33</td>
<td>1996</td>
</tr>
<tr>
<td>Central Italy</td>
<td>1983</td>
<td>6.7</td>
<td>1987</td>
</tr>
<tr>
<td>Belgium</td>
<td>1985</td>
<td>21.5</td>
<td>1993</td>
</tr>
<tr>
<td>Belgium</td>
<td>1995</td>
<td>28.5</td>
<td>1997</td>
</tr>
<tr>
<td>France</td>
<td>1984</td>
<td>26</td>
<td>1990</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>1983</td>
<td>42</td>
<td>1993</td>
</tr>
</tbody>
</table>

In a national survey of 75 laboratories in Belgium, erythromycin resistance rose from 5.5% in 1985 to 21.5% in 1993 [94]. Interestingly, penicillin resistance was low (2%–4%) during this time [94]. Three serotypes (19, 14, and 6) accounted for 80% of macrolide resistance, consistent with clonal spread [94]. From 1995–1997, erythromycin resistance among \textit{S. pneumoniae} in Belgium increased from 24% to 28.5% [74]. In France, macrolide resistance, first detected in 1976, escalated dramatically in the 1980s [112]. A nationwide survey of >8000 isolates from 31 French hospitals documented a rise in erythromycin-resistant strains from 19% in 1984 to 26% in 1990 [112]. By 1992, 27.5% of isolates were resistant to macrolides [119]. These high rates of macrolide resistance occurred when rates of penicillin resistance were low (<1% before 1986; 12% in 1990) [112]. By the late 1990s, 45% of \textit{S. pneumoniae} in southwest France were resistant to erythromycin, but local variability was substantial [120]. In Hungary, macrolide resistance in \textit{S. pneumoniae} rose to 49% in the late 1980s [101]. By the mid-1990s, macrolide resistance rates in Spain [121], Greece [122], Slovakia [123], Bulgaria [124], Rumania [124], Uruguay [125], and some Asian countries [90, 100, 102] exceeded 20%. A survey of 996 isolates of \textit{S. pneumoniae} from 11 Asian countries from 1996–1997 cited widely disparate rates of erythromycin resistance, ranging from 3% (Malaysia) to 89% (Taiwan) [126]. In Hong Kong, erythromycin resistance rose from 0% in 1983 to 42.4% in 1993 [102]. One study from a tertiary hospital in Seoul, Korea, cited macrolide resistance in 37% of clinical isolates of pneumococci [100]. In China and Japan, resistance to macrolides during 1997–1998 exceeded 66% [90, 126] in some countries, macrolide resistance remains uncommon. For example, in South Africa, where multidrug resistance was detected in the 1970s [127], national surveillance at major teaching hospitals from 1987–1990 detected macrolide resistance in only 2.3% of blood or CSF isolates [128]. By the mid-1990s, the rate of macrolide resistance remained <3% in South America.
A recent survey from metropolitan Atlanta had climbed to 31% [78]. Data from the TRUST (Tracking Resistance in the United States) study, which surveys macrolide resistance in the United States, showed that 5.0% of S. pneumoniae isolates from patients (both children and adults) were resistant to macrolides [142]. By 1993–1994, macrolide resistance in metropolitan Atlanta had climbed to 10.4%–11.5% [143]. In a separate national survey from 1992–1993, erythromycin resistance had climbed to 5.0% [142]. By 1993–1994, macrolide resistance rates of 10.4%–11.5% were cited in the United States [143]. For 1992 and 1993 isotopes, rates of resistance in the United States (all age groups) to azithromycin and clarithromycin were 3.2% and 3.5%, respectively [147]. In a separate national survey from 1992–1993, erythromycin resistance had climbed to 5.0% [142]. By 1993–1994, macrolide resistance rates of 10.4%–11.5% were cited in the United States [143]. For 1994–1995, 10% of pneumococci from 30 hospitals in the United States were resistant to macrolides [144]. In a 1994 survey from metropolitan Atlanta, Georgia, 15% of pneumococci isolated from patients (both children and adults) with invasive pneumococcal infections were resistant to erythromycin [99]. By 1999, macrolide resistance in metropolitan Atlanta had climbed to 31% [78]. Data from the TRUST (Tracking Resistance in the United States Today) Study, which surveys >400 medical centers in >40 states, cited rates of clarithromycin resistance among S. pneumoniae of 18% in the 1996–1997 respiratory season [145]. By 1997–1998, 21% and 22% of isolates were resistant to azithromycin and clarithromycin, respectively [91]. Rates of resistance were highly variable (range 3.5%–46.9%) among states [24, 145]. More recent data from the TRUST Study is discussed elsewhere. In another large surveillance study (the SENTRY study), 13% of pneumococci isolated from respiratory sources in the United States in 1997 were resistant to macrolides [25]. By November 1997–April 1998, macrolide resistance in the United States (both respiratory and nonrespiratory isolates) in the SENTRY study was 19% [22]. Consistent with other studies [24, 103, 145], rates of resistance differed markedly among states (range 4%–44%) [22]. When only respiratory isolates of pneumococci from patients with suspected pneumonia were evaluated, SENTRY data cited macrolide resistance rates of 12% in the United States and 13%–15% in Canada [23].

A separate survey of 92 laboratories in the United States for 1996–1997 found macrolide-azalide resistance rates of 12.6%–16%, with striking geographic variability (range, 4%–30%) [103]. Another survey in 1997 of >1400 isolates of S. pneumoniae from outpatients from 36 states in the United States (both adults and children) cited resistance rates of 31% to clarithromycin and azithromycin [146]. In a study by the Centers for Disease Control and Prevention, 15% of clinical isolates from patients with invasive pneumococcal diseases in 1998 were nonsusceptible to erythromycin [21]. In Canada, several surveillance studies from 1993–1998 found lower rates of macrolide resistance (ranging 2.5%–9.3%) [25, 58, 82, 148, 149].

### Table 3. Macrolide resistance in Streptococcus pneumoniae, United States.

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>No. of isolates</th>
<th>Macrolide resistant, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979–1987</td>
<td>5459</td>
<td>0.3</td>
<td>[139]</td>
</tr>
<tr>
<td>1987–1989</td>
<td>487</td>
<td>0.2</td>
<td>[140]</td>
</tr>
<tr>
<td>1991–1992</td>
<td>544</td>
<td>2.2–3.7</td>
<td>[141]</td>
</tr>
<tr>
<td>1992–1993</td>
<td>799</td>
<td>5.0</td>
<td>[142]</td>
</tr>
<tr>
<td>1993–1994</td>
<td>740</td>
<td>10.4–11.5</td>
<td>[143]</td>
</tr>
<tr>
<td>1994</td>
<td>431</td>
<td>15</td>
<td>[99]</td>
</tr>
<tr>
<td>1994–1995</td>
<td>1524</td>
<td>10</td>
<td>[144]</td>
</tr>
<tr>
<td>1996–1997</td>
<td>9190</td>
<td>18</td>
<td>[145]</td>
</tr>
<tr>
<td>1996–1997</td>
<td>4489</td>
<td>12.6–16</td>
<td>[103]</td>
</tr>
<tr>
<td>1997</td>
<td>845</td>
<td>11.7–14.3</td>
<td>[25]</td>
</tr>
<tr>
<td>1997</td>
<td>1476</td>
<td>31</td>
<td>[146]</td>
</tr>
<tr>
<td>1997–1998</td>
<td>1601</td>
<td>17.7–18.9</td>
<td>[22]</td>
</tr>
<tr>
<td>1994–1999</td>
<td>4148</td>
<td>16–32</td>
<td>[78]</td>
</tr>
<tr>
<td>1997–1998</td>
<td>1399</td>
<td>19</td>
<td>[23]</td>
</tr>
</tbody>
</table>

**NOTE.** *a*Includes intermediate and high-grade resistance.

### MULTIDRUG RESISTANCE

Macrolide-resistant strains of *S. pneumoniae* are often resistant to β-lactam antibiotics as well as other antibiotic classes [22, 73, 82, 108, 146]. Conjugate or composite transposons may carry multiple resistance determinants to β-lactam or macrolide antibiotics, tetracyclines, sulfonamides, and chloramphenicol [78]. Multidrug resistance is defined as resistance to antibiotics of at least 3 different classes [127]. In the sentinel report of multidrug resistance from South Africa, an isolate of *S. pneumoniae* was resistant to penicillin, tetracycline, erythromycin, clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), and chloramphenicol [127]. After this initial description [127], multidrug-resistant pneumococci emerged in Spain [150], Hungary [101], France [112], and globally [22, 60, 151, 152]. Currently in the United States, 14%–16% of pneumococci are
multidrug resistant (MDR) [21, 22]. Worldwide, most MDR strains are derived from a few clones, such as the Spanish clone (serotype 23F); the Spanish-French clone (serotypes 6B, 9, and 14); and variants of the Spanish clone (serotypes 19A, 19B, and 19F) [60, 151–154]. The 23F MDR Spanish clone of \textit{S. pneumoniae}, present in North America, Europe, Asia, Latin America, and South Africa, is associated with resistance to chloramphenicol (\textit{cat}+), tetracycline (\textit{tetM}+), and TMP-SMX; 75% of isolates are resistant to macrolides (\textit{mef}E+ or \textit{erm}B+) [60]. In contrast, isolates from the French serotype 9/14 clone, widely present in Europe and South America, are resistant to penicillins and TMP-SMX but usually remain susceptible to macrolides, tetracyclines, and chloramphenicol [60].

Patterns of drug resistance (and prevalence of particular clones) vary among different regions and countries. One study in Hong Kong detected 8 different phenotypes of multidrug resistance [102]. The most common clone was multiply resistant to penicillin, ceftiraxone, chloramphenicol, erythromycin, and tetracycline [102]. In Iceland, a MDR clone serotype 6B exhibited resistance to penicillin, tetracycline, chloramphenicol, and TMP-SMX but was susceptible to erythromycin [153]. Transposons carrying \textit{erm}AM often cohabor \textit{tet}M and a chloramphenicol-resistance determinant [78]. A recent study in the United States cited high rates of resistance to tetracycline (96%) and chloramphenicol (61%) among \textit{erm}B+ pneumococci, whereas \textit{mef}E+ isolates exhibited low rates of resistance to tetracycline (12%) or chloramphenicol (5%) [78]. Others have confirmed that multidrug resistance is more common among pneumococci carrying the \textit{erm}B gene product compared with \textit{mef}E [72] or \textit{mef}A genes [51, 73, 155].

Macrolide resistance rates are much higher among pneumococcal strains displaying penicillin resistance [21, 22, 25, 71, 73, 82, 91, 98, 110, 111, 146, 147, 156]. Typically, macrolide resistance is present in ≤5% of penicillin-susceptible (MIC ≤0.06 µg/mL) strains compared with 48%–70% of strains exhibiting high-grade resistance (MIC ≥2 µg/mL) to penicillin [22, 25, 82, 91, 145]. This relationship has practical importance because macrolides should not be used to treat penicillin-resistant pneumococci unless in vitro tests confirm susceptibility to macrolides. Macrolide resistance may also occur among penicillin-susceptible pneumococci [90, 94, 109, 111, 112, 114]. In China, 72% of pneumococci isolated during 1997–1998 were resistant to macrolides even though 64% were resistant to penicillins or cefuroxime [90]. In Japan, 48% of penicillin-susceptible pneumococci were macrolide resistant [90]. Others have noted high rates of macrolide resistance even in penicillin-susceptible strains [109, 110, 114]. These high rates of macrolide resistance may reflect selection pressure from liberal use of macrolides [59, 97, 98]. Clones of MDR pneumococci exhibiting unusual resistance profiles, but remaining susceptible to penicillin, have also been described [109].

### RISK FACTORS FOR MACROLIDE RESISTANCE

The dominant risk factor for macrolide resistance is previous antibiotic use [59, 73, 92, 94, 96–98]. The prevalence of drug-resistant \textit{S. pneumoniae} (DRSP) is higher in pediatric populations [24, 73, 78, 93, 101, 102, 104, 105], particularly in children with recurrent otitis media [32, 72, 110, 121, 157]. Epidemiological studies of young carriers or children with otitis media cited erythromycin resistance of ≥23% in Spain [32, 121] and 42%–64% in Italy [72, 110, 157]. Risk factors for macrolide-resistant \textit{S. pneumoniae} include the following: age <5 years [73, 100, 104, 105, 107]; day-care center attendance [105, 109, 158]; nonbloodstream source [90, 94, 114]; middle-ear isolates [71, 91, 94, 112, 159]; nasopharyngeal or respiratory isolates [73, 91, 111]; nosocomial acquisition [100, 106–108]; and penicillin resistance [22, 71, 82, 91, 100, 102, 106, 160, 161]. In adults, antimicrobial resistance among pneumococci is more common in insured [21, 39] or affluent populations [75] or in elderly patients receiving multiple antibiotics for exacerbations of chronic bronchitis [16, 162]. These relationships reflect previous antibiotic use in these populations (table 4).

Several population-based studies noted correlations between the prevalence of macrolide resistance among \textit{S. pneumoniae} and overall macrolide consumption in the region or country [73, 92, 97, 98]. Granizo and colleagues [97] assessed the relationship of antimicrobial resistance among \textit{S. pneumoniae} to \β-lactam and macrolide consumption in Spain over 19 years (1979–1997). Antibiotic consumption was expressed in defined daily dosage (defined daily dosage per 1000 inhabitants per day). Significant relationships were found (\textit{P}<.001) between erythromycin resistance (MIC ≥1 µg/mL) and global macrolide consumption (\textit{r} = 0.942) as well as between high-level penicillin resistance (MIC ≥2 µg/mL) and global \β-lactam consumption (\textit{r} = 0.948). Further, the prevalence of high-level penicillin and of erythromycin resistance strongly correlated with each other.

### Table 4. Risk factors for macrolide resistance in \textit{Streptococcus pneumoniae}.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>\textit{Risk factor} for macrolide resistance in \textit{Streptococcus pneumoniae}.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent macrolide use (within 1–3 months).</td>
<td>Penicillin resistance</td>
</tr>
<tr>
<td>Age &lt;5 years or ≥65 years</td>
<td>Attendance in day care centers</td>
</tr>
<tr>
<td>Recurrent otitis media</td>
<td>Middle ear or sinus source</td>
</tr>
<tr>
<td>Recent hospitalization</td>
<td>Certain serotypes (6A, 6B, 14, 23F, 19F)</td>
</tr>
<tr>
<td>High-prevalence geographic locale</td>
<td>Clonal dissemination (hospitals, nursing homes, etc.)</td>
</tr>
</tbody>
</table>

Macrolide-Resistant \textit{S. pneumoniae} for CAP • CID 2002;34 (Suppl 1) • S33
The relationship between erythromycin resistance and macrolide consumption was due mainly to consumption of macrolides taken twice a day \( (r^2 = 0.886) \), but this may simply reflect the fact that b.i.d. macrolides are used most commonly in Spain. Some authors suggest that resistance is more likely to develop with the long-acting macrolides due to low \( C_{min} \) and suboptimal pharmacodynamics \[97, 98, 163\]. Although the relationship between heavy use of macrolides and emergence of resistance seems intuitively obvious, others failed to find correlations between macrolide use and rates of resistance among pneumococci \[164\]. The importance of global (total) antibiotic consumption as a risk factor for antimicrobial resistance among other streptococci (e.g., group A streptococci) is supported by some \[165\], but not all, studies \[166\]. In Finland, a correlation was observed between macrolide consumption and increasing macrolide resistance in vitro among \( S. pyogenes \) (group A streptococci) \[165\]. Implementation of a national policy limiting macrolide consumption led to clear decreases in macrolide resistance \[167\]. In contrast, a report from Quebec, Canada, showed no link between macrolide usage and levels of resistance among group A streptococci in 1998 \[166\]. A recent surveillance study in Canada suggests that macrolide resistance in \( S. pneumoniae \) may be declining, even though consumption of macrolides has increased considerably \[149\].

**CLONAL SPREAD**

Clonal spread is an important mechanism for dissemination of DRSP among hospitals, day-care centers, geographic regions, or even between countries \[35, 50, 60, 72, 78, 100, 107, 109, 110, 153, 154\]. Nasopharyngeal carriage in children is the major reservoir for perpetuation and dissemination of clones of DRSP, not only locally, but globally \[72, 73, 100, 105, 107, 109, 110, 153\]. Resistance patterns differ dramatically not only among geographic regions, but among day-care centers or hospitals within the same city \[168\]. Crowding, as may be observed in day-care centers \[73, 109, 168\], hospitals \[107, 169\], correctional facilities \[170\], homeless shelters \[171\], or chronic care facilities \[172\], facilitates transmission of DRSP. Travel amplifies spread of resistant clones within or between geographic regions, countries, or even continents \[60, 109, 110, 126, 153, 154, 158, 168\]. The pace of transmission is accelerated via selection pressure from antibiotic use. Previous antimicrobial use is a strong risk factor for nasopharyngeal carriage of erythromycin-resistant \( S. pneumoniae \) \[73, 104, 105, 107\]. Macrolide-resistant pneumococci may persist for prolonged periods, even after a single dose of azithromycin \[161\].

In a study from Greece, previous receipt of macrolides or \( \beta \)-lactam antibiotics within 3 months was a strong risk factor for nasal carriage of erythromycin-resistant pneumococci; the association was strongest when macrolides were administered within 1 month \[73\]. In a study from Slovakia, nasopharyngeal carriage of MDR \( S. pneumoniae \) serotype 14 correlated with hospitalization in a specific hospital and receipt of erythromycin or cephalosporins in the previous month \[107\]. In numerous studies, penicillin, macrolide, or multidrug resistance were linked to specific serotypes \[35, 50, 72, 78, 100, 107, 109\]. In central Italy, serotypes 6 and 19 had far higher rates of resistance to erythromycin than other serotypes \[110\]. In Italy, \( \text{meF} \) was strongly associated with serotype 6, whereas \( \text{erm} \) was associated with serogroup 19 \[72\]. Strains of MDR pneumococci (serotype 6) observed in Italy \[110\] were previously described in Greece \[93\], suggesting possible clonal spread. \( \text{ermAM} \) isolates are most often observed with serotypes 6B, 23F, 14, or 19F whereas \( \text{meF} \) are associated with serotypes 14, 6A, or 19F \[78\]. Nosocomial spread of a MDR serotype 14 strain of \( S. pneumoniae \) was implicated as a cause of invasive pneumococcal infections in a community in rural Slovakia \[107\]. Spread of erythromycin resistance via a serotype 14 clone from the United Kingdom to Sweden and Australia was documented \[51\].

**CLINICAL SIGNIFICANCE OF IN VITRO MACROLIDE RESISTANCE**

Although the global increase in macrolide resistance among \( S. pneumoniae \) is disturbing, the clinical impact of these in vitro parameters has not been elucidated \[19, 173, 174\]. Studies correlating in vitro data and clinical outcome are lacking for infections due to \( S. pneumoniae \). However, a recent study in Italy assessed the clinical significance of macrolide resistance in children with pharyngitis due to \( S. pyogenes \) \[175\]. In that study, 43% of 934 strains of \( S. pyogenes \) were resistant to macrolides; none were resistant to penicillins or cephalosporins. Overall microbiological eradication rates were 72% with macrolides; 84% with penicillins; and 83% with cephalosporins. Among patients treated with macrolides, eradication rate was 80% when the infecting organisms were erythromycin susceptible compared with 60% when they were erythromycin resistant \[175\]. However, early clinical failures were cited in only 14 (1.5%) of 934 patients. Among 321 patients treated with a macrolide, only 5 (1.6%) had infections that failed to respond to therapy. The authors also retrospectively surveyed >450,000 case records from 30 Italian pediatric departments from 1990–1996 and found no higher rate of complications from streptococcal infections during that time period (0.13% in 1990 and 0.08% in 1996), despite the fact that the rate of \( S. pyogenes \) resistance to macrolides had increased 10-fold \[175\].

These data suggest that in vitro resistance to macrolides is associated with lower microbiological eradication rates for \( S. pyogenes \), but any impact on clinical success is lacking or inconsequential. It has been argued that susceptibility breakpoints
established in vitro have never been validated clinically [175]. As has been discussed, the clinical significance of in vitro resistance among *S. pneumoniae* (not only for macrolide antibiotics, but other classes of antibiotics as well) is controversial. Prospective, randomized trials designed to assess the clinical significance of antimicrobial resistance (any antibiotic class) among pneumococci are lacking, and for logistical reasons, will never be performed. Extrapolating from retrospective studies of pneumococcal pneumonia [26, 27, 38, 39] or prospective studies of CAP [176–180] fail to confirm a convincing relationship between in vitro resistance and in vivo outcomes. Prospective studies of CAP [178, 180], often performed as part of new drug registration trials, typically exclude patients who are seriously ill, have serious comorbidities, or harbor resistant pathogens. Large retrospective studies of CAP have shown that host factors and comorbidities are key factors influencing mortality [12, 181] but did not address the impact of antimicrobial resistance. Such studies may clarify the value of certain classes of antibiotics (e.g., β-lactam, FQs, aminoglycosides) [12], but too few patients were treated with macrolides alone to evaluate the efficacy of macrolides per se or the impact of macrolide resistance on outcome. Notwithstanding these limitations, anecdotal clinical experience suggests that there has not been a wholesale failure of macrolide treatment for CAP that parallels the rise in in vitro resistance.

**MACROLIDES AS PRIMARY THERAPEUTIC AGENTS FOR CAP**

For the past 4 decades, β-lactam and macrolides antibiotics have been highly efficacious as therapy for CAP (including pneumococcal pneumonia) [1, 10]. Several prospective cohort studies confirm that macrolides are used extensively to treat CAP. In the Pneumonia Patient Outcomes Research Team study conducted in North America during 1991–1994, macrolides were prescribed as a part of therapy to 73% of outpatients and 41% of inpatients with CAP [181, 182]. In a recent multicenter (20 hospitals) study in Canada, >70% of 1113 consecutive patients hospitalized for CAP received a macrolide, usually combined with an injectable cefalosporin [183]. Importantly, clinical success rates have been high when macrolides were used to treat CAP. In the multicenter Canadian study, which compared conventional therapy with levofloxacin monotherapy, outcomes (mortality, quality of life, readmission, complications) were similar irrespective of antibiotic regimen utilized (i.e., β-lactam, FQ, macrolide plus β-lactam) [183]. A retrospective review of 864 immunocompetent adult outpatients with CAP enrolled in the Pneumonia Patient Outcomes Research Team study noted high success rates with macrolides as monotherapy [181]. In that observational study, 546 patients (63%) were ≥60 years of age and had no comorbidity; 381 (37%) were aged >60 years or had ≥1 comorbidities. In the low-risk cohort (age ≤60; no comorbidity), 339 patients (62%) were treated with a macrolide alone (94.4% erythromycin; 5.6% clarithromycin) [181]. No deaths were observed in this group, supporting recommendations from the American Thoracic Society advocating orally administered macrolides in low-risk outpatients with mild to moderate CAP. Among the 318 patients aged >60 years or with ≥1 comorbidity, macrolides (principally erythromycin) were prescribed as monotherapy in 175 patients (55%) [181]. Only 2 (1.1%) of 175 patients treated with a macrolide alone died. Although this study excluded immunocompromised patients, it suggests that macrolides are highly efficacious for treatment of CAP in immunocompetent adults (even older adults with comorbidities). However, this study was performed during 1991–1994, when macrolide resistance among *S. pneumoniae* was low, and included all pathogens (not simply pneumococcal pneumonia). Further, immunocompromised adults were excluded.

Other retrospective analyses support the addition of macrolides among elderly patients with CAP requiring hospitalization [12]. Gleeson et al. [12] examined the hospital records of 12,945 Medicare inpatients (≥65 years of age) hospitalized for CAP between October 1994 and September 1995 to assess the relationship between initial antimicrobial therapy and 30-day mortality. Comparisons were made with patients treated with nonpseudomonal third-generation cephalosporins (e.g., cefotaxime, ceftriaxone, cefixime) alone (the reference group). The 3 most common initial regimens were nonpseudomonal third-generation cephalosporins alone (26.5%); second-generation cephalosporin alone (12.3%); and second- or third-generation cephalosporins plus a macrolide (13.0%). Only 1.8% received a macrolide alone. For the entire population, mortality was 15.3%. The OR for 30-day mortality was 1.0 with the nonpseudomonal third-generation cephalosporin alone (reference group). Importantly, 3 antimicrobial regimens were associated with reduced 30-day mortality rates: combination therapy with a macrolide and a second-generation cephalosporin (OR, 0.71); combination therapy with a nonpseudomonal third-generation cephalosporin plus a macrolide (OR, 0.74); and FQ monotherapy (OR, 0.64). In contrast, mortality was higher in patients receiving an aminoglycoside (OR, 1.22) or β-lactam/β-lactam inhibitor plus a macrolide (OR, 1.77). Mortality was similar to the reference group among patients receiving β-lactam/β-lactam inhibitor alone (OR, 1.07) or a macrolide alone (OR, 1.06). These data suggest that combining a macrolide with a β-lactam adds value, but too few patients were treated with macrolide alone to assess the efficacy of this strategy.

Another study affirms that addition of a macrolide to a cephalosporin reduces mortality in adults with CAP [184]. In that study, consecutive adults with CAP admitted to 72 participating...
hospitals in the United States between 15 November 1996 and 1 March 1997 were prospectively studied. Eighty-two percent were admitted from home; 15% from a nursing home; and 3% unknown. Eighty percent of patients were aged >50 years; 60% had ≥1 comorbidities. The impact of initial antimicrobial therapy on survival and hospital length of stay was assessed [184]. Among the 2963 patients eligible for analysis, 5.5% died. Antimicrobial regimens were diverse. The most common regimen was ceftriaxone (with or without a macrolide) (42%). Only 74 patients (2.5%) were treated with a macrolide alone. Factors associated with a decreased mortality (as assessed by multivariate analysis) were female sex and administration of a second- or third-generation cephalosporin or β-lactam/β-lactam inhibitor combination plus a macrolide (OR, 0.40; P = .007 for nonsevere [non-ICU] CAP). For severe CAP requiring ICU stay, the addition of the macrolide showed no benefit (OR, 1.7; P = .18). In addition to reducing mortality in patients with nonsevere CAP, the use of macrolide/β-lactam combinations was associated with a reduced length of stay in the hospital (P = .0003) [184]. In both of these studies [184], too few patients were treated with macrolides alone to allow definitive conclusions. Another study found that including a macrolide as part of initial therapy for hospitalized patients with CAP reduced hospital length of stay significantly (from 5.3 to 2.8 days) [185], but others found no effect on hospital length of stay [12, 186].

TRIALS OF MACROLIDES FOR CAP

In numerous recent clinical trials of CAP, macrolides were as effective as comparators (β-lactam or FQ antibiotics; clinical success rates of 77%–95% with macrolides [179, 187–190] and 70%–100% with comparators [178, 191–197]). However, in one multicenter randomized trial in Scandinavia, roxithromycin was less effective than sparfloxacin (clinical response rates in 79% and 94%, respectively) [194]. In that study, 14 of 15 patients with pneumococcal pneumonia responded to roxithromycin; most treatment failures were due to Haemophilus influenzae, mixed infections, or no documented etiology [194]. Further, in a randomized, multicenter study of 203 adults with mild to moderate CAP, response rates with orally administered azithromycin and orally administered clarithromycin were 94% and 95%, respectively [198]. Plouffe and colleagues [178] summarized 2 studies comprising 615 adults with CAP requiring hospitalization. The first trial was a comparative, nonrandomized study comparing azithromycin monotherapy with cefuroxime with or without erythromycin. Clinical cure rates (among assessable patients) were similar with both regimens (77% and 74%, respectively) [178]. The second study was an open-label trial of azithromycin monotherapy. Clinical responses were cited in 89% of 84 assessable patients. In both studies, 61 patients had CAP due to S. pneumoniae; 7 (11%) had infections that failed to respond to therapy with azithromycin. Four patients with azithromycin-resistant S. pneumoniae were treated with azithromycin monotherapy; 2 were cured and 2 had infections that failed to respond to therapy.

In another trial of 145 adults with CAP requiring hospitalization, patients were randomized to once-daily azithromycin (administered intravenously or orally) or cefuroxime plus erythromycin [179]. Clinical cure rates were 91% with both regimens. Among patients with pneumococcal pneumonia, clinical cure rates were achieved in 7 of 8 with azithromycin monotherapy and in 19 of 20 with cefuroxime-erythromycin. One patient with azithromycin-resistant S. pneumoniae (MIC 8.0 μg/mL) was cured with azithromycin therapy. Gottfried et al. [199] found similar clinical outcomes among adults hospitalized with pneumococcal pneumonia, irrespective of penicillin or macrolide susceptibilities. Macrolide-nonsusceptible strains were isolated in 27 patients; 40 isolates were susceptible to macrolides. Survival rates were similar for patients with macrolide-susceptible, intermediate-susceptible, or resistant strains (82%, 100%, and 96%, respectively). In the aggregate, these myriad studies affirm that macrolides are highly effective in outpatients with mild to moderate CAP, but they fail to clarify the role (or efficacy) of macrolide monotherapy for severe CAP or for infections due to macrolide-resistant pneumococci.

TRIALS OF MACROLIDES FOR TREATING ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS

Macrolides have generally achieved acceptable cure rates for acute exacerbations of chronic bronchitis (AECB) when S. pneumoniae is isolated [200–202]. However, these studies were performed when rates of macrolide resistance in the United States were low and do not address the efficacy of clarithromycin for macrolide-resistant strains. Many studies of AECB excluded pathogens with preexisting macrolide resistance or previous therapy with macrolides [202–206]. A recent review of 3 comparative clinical trials that used clarithromycin suggested no correlation between in vitro resistance and clinical outcome in AECB [173]. Further, in a prospective study comparing clarithromycin with moxifloxacin for treating AECB, S. pneumoniae was implicated in 36 patients; 3 isolates were resistant to macrolides (MIC 256 μg/L) [207]. All but one of the 36 S. pneumoniae isolates were eradicated or presumed eradicated; the MIC of this isolate was not specified.

In a similar comparison of moxifloxacin with azithromycin, S. pneumoniae was the causative organism in 39 of 567 episodes of AECB [208]. Six isolate were azithromycin resistant; all were eradicated with azithromycin or moxifloxacin therapy. These
WHY IS THERE A DISCREPANCY BETWEEN IN VITRO AND IN VIVO PHARMACOKINETICS AND PHARMACODYNAMICS?

 Favorable pharmacokinetic/pharmacodynamic (PK/PD) parameters [209] and high concentrations of antimicrobials at sites of infections [43, 210] may explain the good clinical outcomes achieved despite MIC values in vitro that appear to be “resistant” or “nonsusceptible” [147, 209]. Concentrations of macrolide antibiotics at sites of infections or within phagocytes are well above the MIC for the infecting organisms. Studies have shown that clinical outcomes correlate better with PK/PD parameters than with MIC values [209]. The most important PK/PD parameters for macrolide antibiotics are not conclusively established. However, most experts suggest that 14-member macrolides (e.g., erythromycin, clarithromycin) are time dependent (i.e., efficacy is linked to the time during which the drug concentration exceeds the MIC for the dosing interval) whereas the azalides (e.g., azithromycin) are concentration dependent (i.e., efficacy is most closely linked to the area under the 24-h serum concentration time curve [AUC] or AUC/MIC ratio) [19, 43, 163, 209, 211, 212]. By use of these PK/PD principles, in vitro susceptibility values for clarithromycin and azithromycin exceed 90% among isolates of *S. pneumoniae* [147]. Additional properties may distinguish specific macrolide antibiotics. According to time-kill curves, erythromycin is bacteriostatic at the MIC and exhibits low bactericidal activity above the MIC, whereas clarithromycin is bactericidal at the MIC and rapidly bactericidal at higher concentrations [213]. Both clarithromycin and azithromycin exhibit longer postantibiotic effects than erythromycin [213, 214].

Further, macrolides achieve high concentrations at sites of infections (including bronchopulmonary sites) [43, 215–219]. High serum levels are important to control intravascular infections (e.g., endocarditis) or infections in sites where antibiotic penetration is poor (e.g., meninges) [19]. By contrast, for treating pneumonia, antibiotic levels in extracellular fluid and alveolar lining fluid are probably more important than serum levels [19]. In normal volunteers, steady-state concentrations of clarithromycin and azithromycin are higher in lung epithelial lining fluid (ELF) than serum [43, 215]. In healthy volunteers, peak intracellular concentrations of 181 µg/mL were achieved within alveolar macrophages 6 h after a single dose of clarithromycin [216]. With repetitive doses of clarithromycin, mean concentrations in ELF and alveolar macrophages were 34.4 and 480 µg/mL compared with plasma levels of only 2.0 [215]. By 24 h, levels in ELF, alveolar macrophages, and plasma were 4.6, 99.4, and 0.23, respectively. Similarly, with azithromycin, concentrations within alveolar macrophages were 20 times greater than serum levels 7 days after institution of therapy [218]. Concentrations of azithromycin in ELF at 4 and 24 h after dosing are lower than with clarithromycin [215].

Penetration of azithromycin into lung tissue is relatively inefficient in normal, healthy volunteers [216, 217], but these studies likely do not apply to patients with bronchopulmonary infections. Azalide concentrations in ELF rise dramatically in response to inflammation [43]. In addition, macrolides and azalides are avidly concentrated within phagocytes (macrophages or leukocytes); intracellular levels greatly exceed the MIC for *S. pneumoniae* [43, 210, 220–222]. High concentrations within leukocytes amplify the effects of macrolides [43]. First, leukocytes are attracted to sites of infection via chemotaxis, where the intracellular load of macrolides is delivered and released directly at the site of infection. Second, leukocytes directly phagocyte pathogens (e.g., pneumococci), thereby exposing them to intracellular reserves of antimicrobial agents. In both cases, the result is to boost the concentrations of antimicrobial in the vicinity of infecting pathogen well above serum levels.

OTHER PROPERTIES OF MACROLIDE ANTIBIOTICS THAT MAY INFLUENCE OUTCOME

Additional properties of macrolide antibiotics may enhance their efficacy in respiratory infections [223]. Erythromycin aids in mobilization of mucus [224] and reduces bronchial hyperreactivity [225] in people with asthma. Clarithromycin normalizes nasal mucus in patients with sinusitis [180] and decreases sputum production [226]. Importantly, macrolides have anti-inflammatory properties, which may attenuate chronic respiratory tract disorders. For example, chronic therapy with low-dose (300–600 mg daily) erythromycin is beneficial for diffuse panbronchiolitis, a disease characterized by chronic sinusitis and bronchiectasis [227–229]. Subsequent studies confirmed benefit with clarithromycin, azithromycin, and roxithromycin [224]. These beneficial effects of macrolides are likely due to mechanisms other than antibacterial activity because the concentrations of antibiotics in tissue are well below the MIC for the relevant infecting organisms (e.g., *H. influenzae* or *Pseudomonas aeruginosa*) [227, 228]. Further, macrolides were more effective than FQs in panbronchiolitis, even though FQs have a far broader antimicrobial spectrum [224, 229]. Anti-inflammatory properties may be important in orchestrating the effect of macrolides in panbronchiolitis. Among patients with panbronchiolitis, treatment with erythromycin decreases or atten-
utes several inflammatory cells or components in bronchoalveolar lavage fluid, including the following: the number of neutrophils [230]; Pseudomonas-induced, neutrophil-derived IL-8 [231]; IL-1β and IL-8 [232]; leukotriene B4 (LTB4) [233]; and neutrophil-derived defensins [224]. Macrolides also modulate lymphocyte function [234] and increase natural killer cell activity in blood [224]. These diverse studies suggest that beneficial effects of macrolides may be orchestrated via both direct antibacterial effects as well as other (nonantimicrobial) mechanism or mechanisms.

**DOES RESISTANCE AFFECT THE “FITNESS” OF THE ORGANISMS?**

Acquisition of antimicrobial resistance genes can decrease the “fitness” of the organisms, either by reducing virulence or viability [235]. Whether this is the case for macrolide-resistant *S. pneumoniae* is not known. Several surveillance studies cited lower rates of antimicrobial resistance (typically penicillin or cephalosporin resistance) among pneumococcal isolates from blood or CSF [26, 27, 38, 39]. Reduced virulence seems unlikely because invasive pneumococcal infections due to penicillin- or cephalosporin-resistant pneumococci are associated with mortality rates as high or higher when compared with susceptible strains [26, 27, 38, 39]. Is the viability of the organisms compromised by acquisition of antimicrobial resistance genes? This seems unlikely because prolonged persistence of macrolide-resistant pneumococci has been documented [161]. Bacteria can usually adapt over time or serial passage to functional or physiological deficit or deficits associated with antimicrobial resistance genetic mutations [235]. Overall, resistance confers a survival advantage, which is amplified by selection pressure from antibiotic use.

**CLINICAL EXAMPLES OF MACROLIDE FAILURES IN VIVO**

Despite favorable PK/PD properties of the macrolides and azalides, an increasing number of reports in the literature link treatment failures to macrolide resistance in *S. pneumoniae*. Initially, a few anecdotal case reports of clinical failures of macrolides-azalides for meningitis [236, 237] were cited. Subsequent studies (discussed below) cited treatment failures for community-acquired respiratory infections due to macrolide-resistant pneumococci.

1. Lonks and Medeiros [238] described a previously healthy 32-year-old man with CAP who worsened after taking orally administered erythromycin as an outpatient for 3 days. Blood cultures grew erythromycin-resistant *S. pneumoniae*. He responded to intravenously administered penicillin. This prompted a review of the prevalence of erythromycin resistance among bloodstream isolates of *S. pneumoniae* at 2 Rhode Island hospitals. Review of records from January 1990 to 30 June 1991 identified 4 patients with erythromycin-resistant pneumococcal bacteremia, but data regarding clinical course or antibiotic therapy were not provided.
   2. Moreno and colleagues [108] prospectively assessed the clinical significance of macrolide-resistant *S. pneumoniae* at one large hospital. Over a 27-month period (January 1988–March 1990), all hospitalized patients with *S. pneumoniae* in any clinical sample were identified and prospectively followed. Overall, 32 (12.0%) of 269 clinical isolates were resistant to erythromycin. Twenty-seven infections due to erythromycin-resistant *S. pneumoniae* were detected; 5 patients were considered colonized. Mortality rates related to pneumococcal infections were similar in patients with erythromycin-resistant (18%) or erythromycin-susceptible strains (14%). Of patients infected with erythromycin-resistant strains, 5 died (3 had meningitis and 2 had pneumonia). Twenty patients with pneumonia caused by erythromycin-resistant pneumococci were analyzed according to treatment received. Three died within 48 h, precluding assessment. All 9 treated with third-generation cephalosporins were cured; 1 of 2 treated with ampicillin or cotrimoxazole died. Six were treated with erythromycin alone; 4 (3 of whom had bacteremia) were cured. Among the 2 patients whose infections failed to respond to erythromycin, the infection of one was cured with cefotaxime. Cure rates were similar among patients receiving erythromycin or “adequate” antibiotics (*P* = .1). Because of the small sample size and confounding factors, these data are inadequate to assess the impact of erythromycin resistance on clinical outcome. However, it is plausible that the lack of statistical significance reflects a β error (i.e., inadequate sample size).
   3. Treatment with erythromycin failed to clear the infection in 2 of 3 patients hospitalized with CAP caused by macrolide-resistant *S. pneumoniae* [239].
   4. A review of medical records of 2 hospitals in Barcelona, Spain, and Providence, Rhode Island, detected 57 blood isolates of *S. pneumoniae* exhibiting resistance to macrolides [240]. Twelve patients had been treated with macrolides yet developed breakthrough bacteremia. Eleven of these 12 had CAP. Macrolides used in these 12 patients included the following: erythromycin (*n* = 3), azithromycin (*n* = 4), clarithromycin (*n* = 3), and josamycin (*n* = 2). All 9 isolates from Barcelona expressed the ermB determinant; 1 of 3 isolates from Providence had the mefE determinant. Cures were achieved in all 12 patients with β-lactam therapy.
   5. Fogarty and colleagues [241] described 3 adults seen within a 9-month period who received 3–5 days of orally administered azithromycin and were subsequently admitted with bacteremic CAP caused by macrolide-resistant *S. pneumoniae*. Importantly, 2 were previously healthy nonsmokers; the third
CONCLUSIONS AND RECOMMENDATIONS

Regardless of therapy or pathogen resistance, a fraction of patients with pneumococcal pneumonia have infections that fail to respond to treatment (even with appropriate antibiotics). Fatality rates for bacteremic pneumococcal pneumonia range 6%-30% [243]. Clinical failures often reflect factors independent of antimicrobial susceptibility of the infecting organisms. Host factors (e.g., extremes of age, underlying immunosuppressive or debilitating disease, comorbidities) or factors that affect intrinsic virulence of the organisms (e.g., capsular subtype) strongly influence prognosis [243]. Mortality rates are higher in the presence of the following: multilobar involvement; renal insufficiency; need for ICU care; hypoxemia; severe derangement in physiologic parameters; and other comorbidities [1, 4, 5, 11].

Given these confounding factors, assessing the impact of antimicrobial resistance on clinical outcomes is difficult, if not impossible. Prospective, randomized, clinical trials comprising large populations are optimal to address the importance of in vitro resistance on clinical outcomes, but for logistical reasons, they will not be performed. Retrospective studies and case reports are less rigorous and less reliable, but they provide important clinical insights. Although clinical failures with macrolide antibiotics may be meaningless by themselves, failure followed by successful resolution with another antimicrobial strongly suggests clinical significance. In the various studies cited above, the infections of 21 patients with bacteremic pneumococcal infections that failed to respond to therapy with macrolides subsequently respond to other antibiotics (e.g., penicillin, cephalosporins, FQs) [240].

As macrolide-resistant pneumococci become endemic in communities, additional treatment failures can be expected. Current rates of macrolide resistance do not warrant moving away from this class of antimicrobials for most patients with CAP. We believe orally administered macrolides alone remain the drugs of choice for mild to moderate CAP not requiring hospitalization in previously healthy young adults with no risk factors for antibiotic resistance. However, CAP requiring hospitalization warrants a broader spectrum (i.e., either combination therapy with a β-lactam/macrolide or monotherapy with a respiratory FQ). Further, given the inability to predict antibiotic resistance de novo, we do not use macrolides for fulminant or life-threatening CAP. In this context, we administer a β-lactam plus a respiratory FQ. Further, when significant comorbidities or risk factors for DRSP exist, consideration should be given to the respiratory FQs to treat not only CAP but also AECB. Most importantly, reducing the overall use of antibiotics is critical to curtail the escalation of antimicrobial resistance. Use of antimicrobials for viral upper or lower respiratory tract infections should be discouraged. Finally, vaccination of high-risk populations is advised.

Vaccination of high-risk patients (both children and adults) may reduce the incidence of invasive pneumococcal infections [244, 245] and nasopharyngeal carriage [246]. Because ~50% of macrolide resistance among pneumococci are in children <5 years of age [78], the use of the conjugate vaccine in young children [245, 247] may be critical to reduce nasopharyngeal carriage [246] and limit dissemination of drug-resistant strains. The use of the 23-valent polysaccharide vaccine in selected adult populations reduces the frequency of invasive pneumococcal infections [244] but is underutilized. The 23-valent vaccine encompasses most serotypes responsible for penicillin or macrolide resistance. The 7-valent conjugate vaccine for use in children contains pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F [245], and thus encompasses most strains responsible for macrolide resistance. Serotype 6A accounts for ~20% of mefE-associated erythromycin resistance in children <5 years old [78]. Because serotype 6B is included in the 7-valent conjugate vaccine, this may provide cross-protective antibodies [248].
References


10. Lynch and Martinez


198. O’Doherty B, Muller O. Randomized, multicentre study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment
239. Aubier M, Doe H, Gialdroni-Grassi G. Sparfloxacin for the treatment of...


