**ABSTRACT**

In the United States, respiratory tract infections (RTIs) are associated with millions of office visits each year. The initial pharmacological management of these relatively common infections is usually empirical. Antibacterial therapy for RTIs must be active against common pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, as well as atypical pathogens, *Legionella* spp, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. Efficacy and safety of beta-lactam, macrolide, fluoroquinolone, and ketolide antibiotics used to treat RTIs, including potential drug interactions, are reviewed. Ketolides represent a new class of semisynthetic antimicrobials that were derived from erythromycin A. Structural changes affecting bacterial resistance that have been incorporated into telithromycin, the first ketolide approved in the United States, are described. Recently published surveillance data indicate that the incidence of penicillin- and multidrug-resistant *S pneumoniae* has steadily increased in North America and efforts to slow this increase are reviewed. Data from the first 3 years of the Prospective Resistant Organism Tracking and Epidemiology of the Ketolide Telithromycin—United States surveillance study suggest that penicillin and erythromycin resistance among isolates of *S pneumoniae* have remained high, approximately 20% to 30%, respectively. Pharmacists need to take an active approach in the judicious use of antimicrobial therapy for RTIs, including the use of no antibiotic in cases of viral or self-limiting infection. When antimicrobial therapy is warranted, treatment should be individualized taking into account prior antimicrobial therapy, concomitant medications, and the medical history of the patient. (Adv Stud Pharm. 2005;2(6):219-230)

Respiratory tract infections (RTIs) account for about 50 million deaths worldwide each year.1 Management of RTIs presents a significant burden on the healthcare system in the United States as these infections account for about 112 million office visits annually.2 Appropriate treatment for these relatively common infections has proven to be challenging. The majority of RTIs are viral in nature; however, about 75% of all antibiotic use is for the treatment of these infections.3 The most common RTIs in the United States include acute rhinosinusitis, acute exacerbations of chronic bronchitis (AECB), and community-acquired pneumonia (CAP).4 Each year, CAP is responsible for approximately 10 million physician visits, 500 000 hospitalizations, and 45 000 deaths in the United States.5

The 3 most common bacterial pathogens that cause the majority of community-acquired RTIs are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.6,7 An additional group of atypical pathogens account for significant morbidity and mortality associated with CAP: *Legionella* spp, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. Appropriate management of these prevalent infec-
tions is multifaceted and includes considerations for improving therapeutic outcomes, reducing the emergence and prevalence of bacterial resistance, and minimizing costs of therapy.\(^3\) The focus of this review will be the pharmaceutical management of community-acquired RTIs, specifically sinusitis, AECB, and CAP.

**Selection of Appropriate Antibiotic Therapy**

The selection of the most appropriate antibiotic is key when treating patients with a bacterial RTI; however, the choice of initial therapy in the treatment of RTIs is usually made without the benefit of knowing the pathogen or the antibiotic susceptibility of the pathogen. The most appropriate agent should obviously provide coverage for common pathogens but should also possess a “tailored” spectrum of activity. A tailored spectrum of activity indicates that the agent covers common pathogens that are likely to be the cause of the infection being treated, but has limited or no coverage for microbes that are not likely to be the cause of infection. An ideal antibiotic with tailored activity for an RTI would have limited or no effect on nonrespiratory, enteric gram-negative organisms but would have excellent activity against the most common pathogens encountered in RTIs.\(^4\)

As most antibiotic treatment of RTIs is empirical, an understanding of which agents provide coverage for the common bacterial pathogens in RTIs is important. Coverage of the typical respiratory pathogens (\(S\) pneumoniae, \(H\) influenzae, and \(M\) catarrhalis) is generally achieved by beta-lactams, fluoroquinolones, ketolides, and macrolides. Atypical pathogens are susceptible to fluoroquinolones, ketolides, and macrolides, but not to beta-lactams. Coverage of the likely pathogens may not be sufficient as the most appropriate antibiotic must also be effective against resistant strains of typical pathogens for patients with risk factors for resistant strains. Clinicians should recognize the risk factors for infection with penicillin- and/or multidrug-resistant \(S\) pneumoniae (MDRSP) including previous use of broad-spectrum antibiotics, carriage of \(S\) pneumoniae, daycare attendance, exposure to children who attend daycare, severe comorbidities, immunosuppression, and high intake of alcohol.\(^5,10\) RTIs caused by strains of \(S\) pneumoniae resistant to penicillin, macrolides, or fluoroquinolones have resulted in poor clinical outcomes.\(^15,16\)

**Comparison of Antibiotic Classes**

**Beta-Lactams**

Although not useful in the treatment of atypical infections, beta-lactams are commonly prescribed for the treatment of RTIs. Data from the Canadian Bacterial Surveillance Network has shown that there has been an increase in resistance among \(S\) pneumoniae to penicillin from 0% in 1988 to 7% in 2001.\(^17\) In the United States, penicillin resistance has also increased over this time period, but the prevalence of penicillin-resistant \(S\) pneumoniae is much higher compared with Canada. The Prospective Resistant Organism Tracking and Epidemiology of the Ketolide Telithromycin—United States (PROTEKT US) surveillance study, which evaluated the susceptibility of 10,103 strains of \(S\) pneumoniae collected in the United States during the 2000-2001 respiratory season, reported that 26.3% of these pneumococcal isolates were resistant to penicillin.\(^17\) However, data from 2001 to 2002 (10,012 strains) and 2002 to 2003 (10,886 strains) suggest that \(S\) pneumoniae resistance to penicillin has declined slightly to 21.2% and 20.2%, respectively. Susceptibility data from PROTEKT US 2000 to 2003 also indicated that approximately 4% of these isolates were resistant to amoxicillin-clavulanate, but 23% to 29% were resistant to cefuroxime.\(^18\) Although amoxicillin-clavulanate was studied in PROTEKT US, it should be emphasized that the in vitro activity of amoxicillin is comparable with amoxicillin-clavulanate for \(S\) pneumoniae because the mechanism of beta-lactam resistance is not beta-lactamase production. Therefore, amoxicillin should be equally efficacious in treating pneumococcal infections as amoxicillin-clavulanate.

The prevalence of MDRSP was stable at approximately 31% over the first 3 years of the PROTEKT US study.\(^19\) A clear relationship has been observed between the increasing prevalence of penicillin resistance among respiratory tract isolates of \(S\) pneumoniae and resistance to other beta-lactam agents, macrolides, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole.\(^17,20\) Amoxicillin-clavulanate resistance is very low (0.03%) for penicillin-susceptible isolates, but 16.6% of penicillin-resistant isolates are cross-resistant to this agent.\(^20\) As supported by data from the SENTRY Antimicrobial Surveillance Program, the vast majority of penicillin-resistant pneumococci are cross-resistant to the oral cephalosporins.\(^19\) In the PROTEKT US study, 97.9%
of penicillin-resistant *S. pneumoniae* strains were cross-resistant to cefuroxime. This association between penicillin resistance and diminished cephalosporin activity is due to alterations in common penicillin-binding-protein targets of action for both classes of antimicrobials.

**Macrolides**

Two factors have largely influenced the frequent use of macrolides in the treatment of RTIs. First, macrolide-resistant *S. pneumoniae* was relatively uncommon in the past, and many prescribers do not consider macrolide resistance to be clinically relevant. Secondly, macrolides have excellent activity against atypical pathogens. Macrolides are commonly used for RTIs in place of penicillins and are currently recommended as first-line empirical therapy for CAP in certain patient populations, primarily those without risk factors for MDRSP.

Macrolide resistance in *S. pneumoniae* has increased dramatically in the United States since the early 1990s. In one study, macrolide resistance increased from 10.3% in 1994 to 26.2% in 1999 to 2000. According to data from the Tracking Resistance in the United States Today (TRUST) study, azithromycin resistance in *S. pneumoniae* during the 1998 to 1999 respiratory season was 23.0% compared with 28.0% during the 2000 to 2001 season. Surveillance data from PROTEKT US demonstrated that 31% of pneumococcal isolates in 2000 to 2001 were resistant to azithromycin, clarithromycin, and erythromycin. The prevalence of macrolide resistance in this surveillance study has remained stable at 28% in 2001 to 2002, and 29% in 2002 to 2003. In addition, a strong association has been observed between penicillin and macrolide resistance. For example, 78% of penicillin-resistant strains of *S. pneumoniae* in the PROTEKT US study were also resistant to erythromycin, azithromycin, and clarithromycin. Of interest, approximately 6.5% of penicillin-susceptible pneumococci are resistant to the macrolides. Therefore, clinicians should monitor for the potential of a macrolide clinical failure in patients without risk factors for MDRSP.

Two mechanisms are primarily responsible for the majority of pneumococcal resistance to the macrolides. The first resistance mechanism is an active efflux pump, which is mediated by the *mef*(A) gene and confers low-level resistance to the macrolides (minimum inhibitory concentrations [MICs] 1-16 mg/L). However, *mef*(A) strains remain susceptible to clindamycin. The second resistance mechanism is the modification of the macrolide ribosomal target by a methylase enzyme. This mechanism is mediated by the *erm*(B) gene and confers high-level resistance to the macrolides and clindamycin ([MICs] 32 mg/L). Efflux is the most common mechanism of macrolide resistance in pneumococcal isolates in the United States. The prevalence of isolates that possess both resistance mechanisms is increasing. Overall, 9.7% of macrolide-resistant pneumococci in 2000 to 2001 possessed both *erm*(B) and *mef*(A) genes compared with 16.4% of macrolide-resistant isolates in 2002 to 2003. The prevalence of isolates with both resistance mechanisms was highest in children under 2 years of age (23.9%) followed by children 3 to 14 years of age (20.5%).

It has been proposed that an important factor in the increasing prevalence of macrolide resistance in *S. pneumoniae* may be the use of long-acting macrolides. Countries with the highest consumption of macrolides have the highest overall prevalence of macrolide-resistant pneumococci. When plotted against the consumption of long-acting macrolides, a linear increase in macrolide resistance has been observed (*r* = 0.896). In the United States, the increase in the number of clarithromycin and azithromycin prescriptions was highly correlated with the increased incidence of pneumococcal resistance to both agents. A strong positive correlation between azithromycin use and macrolide resistance (*r* = 0.9659, *P* <.0001) has also been demonstrated in Canada. In a recent Canadian study, prior use of azithromycin and clarithromycin within the preceding 3 months was associated with invasive pneumococcal infections caused by macrolide-resistant strains; however, the association was stronger for azithromycin. Prior azithromycin use was associated with a more than 4- to 10-fold increase in the likelihood that the infecting isolate would be macrolide-resistant. Fifty-three percent of patients receiving azithromycin within the preceding 3 months had a macrolide-resistant pneumococcal infection upon hospital admission. However, prior erythromycin use was not associated with infecting strains that were resistant to any drug class.

A potential explanation for these findings may be found when comparing the in vitro potency and pharmacokinetics of the macrolides. Azithromycin is 2- to
4-fold less active against *S. pneumoniae* than clarithromycin or erythromycin. In addition, serum azithromycin concentrations, regardless of dosing strategy, are dramatically lower and the half-life of azithromycin (approximately 68 hours) is significantly longer than the other macrolides. Although tissue (intracellular) concentrations of all macrolides are high, it should be noted that *S. pneumoniae* is an extracellular pathogen. In general, serum concentrations of unbound (free) drug are predictive of extracellular concentrations. Therefore, use of the least potent macrolide (highest MICs) with the lowest serum concentrations and longest half-life will potentially lead to prolonged, subinhibitory drug exposure to the pathogen and a greater propensity to select for macrolide-resistant *S. pneumoniae*. The selective pressure for resistance may be reduced if more potent, shorter-acting macrolides are used preferentially.

Despite the high prevalence of macrolide resistance in *S. pneumoniae*, published reports of macrolide clinical failures in RTIs have been relatively uncommon. However, most published case studies have only identified macrolide treatment failures that resulted in breakthrough bacteremia and hospitalization. Nonbacteremic pneumococcal pneumonia is 3 to 5 times more common than bacteremic pneumonia, and macrolide monotherapy is more commonly prescribed in the outpatient setting where culture and susceptibility testing are rarely performed, even in the case of treatment failure. If an outpatient fails to respond or relapses during macrolide therapy, it is not known whether the patient was infected with a resistant pathogen initially, whether the pathogen developed resistance during therapy, or whether the infection had a nonbacterial etiology. Therefore, the published reports of macrolide treatment failures may only represent the tip of the iceberg. There is increasing evidence of bacteriologically confirmed macrolide failures in pneumococcal pneumonia if the macrolide MIC is 4 mg/L or greater. These data are clinically important considering the increasing prevalence of pneumococci that harbor both macrolide resistance mechanisms, resulting in high-level macrolide resistance (MIC ≥32 mg/L). A proposed explanation for the lack of macroide clinical features in resistant pneumococcal infections has been that macrolides achieve high concentrations in respiratory tissues and fluids, such as epithelial lining fluid (ELF), relative to the concomitant serum concentrations. ELF bathes the terminal bronchioles and alveoli in the lungs and may be the primary site of extracellular respiratory pathogens, such as *S. pneumoniae*. When azithromycin was dosed at 500 mg on Day 1 followed by 250 mg/day for the next 4 days, plasma and ELF concentrations achieved 4 hours after dosing on Day 5 were 0.08 ± 0.05 mg/L and 1.01 ± 0.45 mg/L, respectively. After 500 mg every 12 hours for 9 doses, clarithromycin concentrations achieved 4 hours after the last dose were 2.00 ± 0.60 mg/L in serum and 34.5 ± 29.3 mg/L in ELF. Using an in vitro pharmacodynamic model, azithromycin and clarithromycin eradicated macrolide-susceptible strains at clinically achievable serum and ELF concentrations. However, macrolide-resistant pneumococci were not eradicated at either serum or ELF concentrations of azithromycin, regardless of the resistance phenotype (*mef*A or *erm*B). Clarithromycin eradicated macrolide-resistant strains at clinically achievable ELF concentrations, but only for isolates with the *mef*(A) phenotype and MICs 8 mg/L or less. Clarithromycin ELF concentrations did not eradicate the macrolide-resistant strain with the *erm*(B) phenotype. Therefore, clarithromycin may be effective in the treatment of lung infections caused by macrolide-resistant strains with the *erm*(B) phenotype or by macrolide-resistant pneumococci demonstrating efflux-mediated resistance, but clinical data are lacking.

**Fluoroquinolones**

As the prevalence of beta-lactam and macrolide resistance among pneumococci has increased, the use of fluoroquinolones for the empirical treatment of RTIs in adults has increased dramatically. In general, respiratory fluoroquinolones (eg, levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin) possess in vitro activity against *S. pneumoniae*, including strains resistant to penicillin and macrolides. As a result, fluoroquinolones are currently recommended as first-line agents for monotherapy of CAP in patients with risk factors for resistant pneumococci, specifically multiple underlying comorbidities and patients receiving antibiotic therapy in the previous 3 months. However, fluoroquinolones are frequently used to treat RTIs in patients who have no risk factors for infection with drug-resistant *S. pneumoniae*. The overuse of fluoroquinolones in these patients raises serious concerns about the development of bacterial resistance and may threaten the clinical utility of this drug class in the future.
Fluoroquinolones exhibit concentration-dependent bactericidal activity; therefore, the goal of a dosing regimen is to maximize the achievable drug concentrations in relation to the MIC for the offending bacterial pathogen. The 24-hour area under the serum concentration-time curve (AUC)/MIC ratio has been shown to be the best parameter for predicting clinical and bacteriologic outcomes for this antimicrobial class. Data from in vitro pharmacodynamic (PD) models suggests that free 24-hour AUC/MIC ratios of 30 to 60 are sufficient for eradication of *Streptococcus pneumoniae*.41-44

Fluoroquinolone PD against pneumococci has also been evaluated in 58 adult patients with CAP or AECB.45 A free-drug AUC/MIC ratio of below 33.7 was associated with a probability of microbiological response of 64% compared with a 100% probability of microbiological response observed with AUC/MIC ratios above 33.7 (P = .01).45 However, a recent study has suggested that a free AUC/MIC ratio 100 or above may be needed to protect against the selective enrichment of resistant mutants of *Streptococcus pneumoniae*.46 These data provide further support for the use of PD parameters in selecting the most appropriate fluoroquinolone for treatment of RTIs. The AUC/MIC ratios for the respiratory fluoroquinolones and ciprofloxacin against *Streptococcus pneumoniae* are presented in Table 1.41-44,47-50

Over the past 5 years, fluoroquinolone resistance in *Streptococcus pneumoniae* has begun to emerge in the United States, but high-level fluoroquinolone resistance remains low.17,18,20 Fluoroquinolones exert their antibacterial activity by inhibiting DNA replication, forming cleavage complexes with DNA gyrase and/or topoisomerase IV. The gyrase *A* gene encodes for the A subunit of DNA gyrase, and the par*C* gene encodes for the C subunit of topoisomerase IV. In general, fluoroquinolone resistance occurs in a stepwise fashion with a mutation in either gyrase *A* or par*C* appearing first, followed by acquisition of a second mutation in the other target site.50,51 High-level fluoroquinolone resistance is observed in pneumococcal isolates that harbor mutations in both gyrase *A* and par*C* target sites. However, isolates with a single first-step mutation will likely be reported as susceptible to fluoroquinolones by microbiology laboratories because the modest increase in MIC is not sufficient for the isolate to be classified as resistant. Emergence of resistance during fluoroquinolone therapy is more likely to develop in isolates that harbor a first-step mutation in one of the target genes at the beginning of therapy since only one additional mutation is required for high-level resistance to occur. In a recent survey of more than 1800 pneumococcal isolates in the United States, high-level fluoroquinolone resistance was seen in 2% of strains, but approximately 20% of the isolates harbored at least one mutation in either the gyrase *A* or par*C* genes.46

Several factors are associated with fluoroquinolone resistance in *Streptococcus pneumoniae*. In the United States, increased levofloxacin use has been associated with decreased pneumococcal susceptibility to levofloxacin.52 In Canada, infections with fluoroquinolone-resistant *Streptococcus pneumoniae* have been associated with previous use of fluoroquinolones, current residence in a nursing home, and nosocomial acquisition of the pneumococcal infection.31 In patients who acquired their infection in a nursing home and had received a fluoroquinolone in the previous 3 months, the prevalence of pneumococcal resistance to levofloxacin, gatifloxacin, and moxifloxacin was 23%,

### Table 1. AUC, MIC, and AUC/MIC Ratios for Respiratory Fluoroquinolones for *Streptococcus pneumoniae*

<table>
<thead>
<tr>
<th>FQ</th>
<th>% Protein Binding</th>
<th>Total (Free) AUC mg* h/L</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; mg/L</th>
<th>Total (Free) AUC/MIC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (750 mg twice daily)</td>
<td>~30</td>
<td>31.6 (22.1)</td>
<td>2.0</td>
<td>15.8 (11.1)</td>
</tr>
<tr>
<td>Gatifloxacin (400 mg/day)</td>
<td>~20</td>
<td>51 (40.8)</td>
<td>0.5</td>
<td>102 (81.6)</td>
</tr>
<tr>
<td>Levofloxacin (500 mg/day)</td>
<td>~35</td>
<td>47.5 (30.9)</td>
<td>1.0</td>
<td>47.5 (30.9)</td>
</tr>
<tr>
<td>Levofloxacin (750 mg/day)</td>
<td>~35</td>
<td>90.7 (59)</td>
<td>1.0</td>
<td>90.7 (59)</td>
</tr>
<tr>
<td>Moxifloxacin (400 mg/day)</td>
<td>~50</td>
<td>48 (24)</td>
<td>0.25</td>
<td>192 (96)</td>
</tr>
<tr>
<td>Gemifloxacin (320 mg/day)</td>
<td>~60</td>
<td>9.1 (3.6)</td>
<td>0.06</td>
<td>152 (61)</td>
</tr>
</tbody>
</table>

AUC = area under the curve; FQ = fluoroquinolone; MIC<sub>90</sub> = minimum inhibitory concentration at which 90% of isolates are inhibited.

Data from Lacy et al;51 Lister and Sanders; Garrison; Goldstein and Garabedian-Ruffalo; Killion; Allen et al; Jacobs et al; Doern et al.
23%, and 14%, respectively. Therefore, monotherapy with a respiratory fluoroquinolone should be used with caution, if at all, in residents of long-term care facilities who are diagnosed with pneumonia, especially if they have been previously treated with fluoroquinolones.

A review of reported cases of fluoroquinolone treatment failures for RTIs due to fluoroquinolone-resistant *S. pneumoniae* was recently published. Overall, 20 ciprofloxacin and levofloxacin treatment failures were identified, including 1 sinusitis case, 12 cases of CAP, 5 cases of AECB, and 2 cases of hospital-acquired pneumonia. Clinical failures were related to the presence of fluoroquinolone-resistant *S. pneumoniae* at the start of therapy or the emergence of resistance during therapy. Risk factors for clinical failure for pneumococcal RTIs with a fluoroquinolone included advanced age, comorbid conditions, and a history of recent fluoroquinolone exposure.

**Ketolides**

Derived from erythromycin A, the ketolides represent a new class of semisynthetic antimicrobials. Telithromycin was approved by the US Food and Drug Administration (FDA) on April 1, 2004, and represents the first ketolide approved in the United States. Telithromycin’s pharmacokinetic (PK) properties and tissue/plasma concentrations are displayed in Tables 2 and 3. Important structural changes have been incorporated into ketolide compounds to improve their activity and PK parameters compared with their parent drugs. Although derived from 14-membered ring macrolides, the ketolides differ in that they have a carbonyl group at the C-3 position rather than a cladinose sugar resulting in ketone functionality and a low potential for induction of resistance via the *erm*(B) gene. Besides ketolides, all other 14- and 15-membered ring antibiotics are able to induce methylase activity in streptococcal strains (MLSs resistance). Telithromycin has a high binding affinity for the 50S ribosomal subunit thus allowing it to retain activity against pathogens with inducible methylase activity. Compared with macrolides, telithromycin does not effectively induce the efflux pump, a common mechanism of resistance for 14- and 15-membered ring antibiotics.

Telithromycin exhibits concentration-dependent bactericidal activity and excellent in vitro activity against a variety of common respiratory pathogens (Table 4). Overall, telithromycin resistance among strains of *S. pneumoniae* in PROTEKT US was 0.04% in 2000 to 2001, 0.02% in 2001 to 2002, and 0.01% in 2002 to 2003. Telithromycin is also active against over 99% of penicillin-resistant and macrolide-resistant pneumococci, regardless of the mechanism of macrolide resistance. From 2000 to 2003, 99.6% of *mef*(A), 98.4% of *mef*(B), and 98.2% of *erm*(B) strains were susceptible.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single Dose (n = 18)</th>
<th>Multiple Dose (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>1.9 (0.80)</td>
<td>2.27 (0.71)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)*</td>
<td>1.0 (0.5-4.0)</td>
<td>1.0 (0.5-3.0)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-24)&lt;/sub&gt; (µg•h/mL)</td>
<td>8.25 (2.6)</td>
<td>12.5 (5.4)</td>
</tr>
<tr>
<td>Terminal t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>7.16 (1.3)</td>
<td>9.81 (1.9)</td>
</tr>
<tr>
<td>C&lt;sub&gt;24h&lt;/sub&gt; (µg/mL)</td>
<td>0.03 (0.013)</td>
<td>0.07 (0.051)</td>
</tr>
</tbody>
</table>

*Median (min-max) values.
AUC = area under concentration vs time curve; C<sub>24h</sub> = plasma concentration at 24 hours postdose; C<sub>max</sub> = maximum plasma concentration; SD = standard deviation; t<sub>1/2</sub> = terminal plasma half-life; T<sub>max</sub> = time to C<sub>max</sub>.

<table>
<thead>
<tr>
<th>Mean Concentration (µg/mL)</th>
<th>Hours Postdose</th>
<th>Tissue or Fluid</th>
<th>Plasma Ratio</th>
<th>Tissue/Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial mucosa</td>
<td>2</td>
<td>3.88*</td>
<td>1.86</td>
<td>2.11</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1.41*</td>
<td>0.23</td>
<td>6.33</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.78*</td>
<td>0.08</td>
<td>12.11</td>
</tr>
<tr>
<td>Epithelial lining fluid</td>
<td>2</td>
<td>14.89</td>
<td>1.86</td>
<td>8.57</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3.27</td>
<td>0.23</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.84</td>
<td>0.08</td>
<td>14.41</td>
</tr>
<tr>
<td>Alveolar macrophages</td>
<td>2</td>
<td>65</td>
<td>1.07</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>100</td>
<td>0.605</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>41</td>
<td>0.073</td>
<td>540</td>
</tr>
</tbody>
</table>

*Units in mg/kg.
**DRUG-DRUG INTERACTIONS**

**BETA-LACTAMS**

Although relatively uncommon, beta-lactam antibiotics may be associated with some potentially serious drug interactions. For example, plasma concentrations of cefaclor, cephalaxin, and cefpodoxime may be reduced with antacids, H₂ antagonists, and iron supplements. Large doses of penicillin antibiotics can increase the risk of bleeding in patients on anticoagulants. A variety of antibiotics, including beta-lactams, have been implicated in a drug interaction with oral contraceptives resulting in decreased efficacy of the contraceptive due to interruption of the enterohepatic circulation of estrogen. However, no definitive studies have demonstrated contraceptive failure from such a drug interaction.

**MACROLIDES**

Traditional macrolide antibiotics, such as erythromycin, are associated with significant drug interactions due to their affinity for and inhibition of cytochrome P (CYP) 450 isoenzymes, thus causing altered metabolism of other agents with a similar metabolic pathway. Erythromycin is extensively metabolized by CYP3A isozymes. Agents that inhibit CYP3A isozymes (e.g., cimetidine, diltiazem, amiodarone, protease inhibitors, and the “azole” antifungals [ketoconazole, itraconazole, fluconazole]) have the potential to increase plasma erythromycin concentrations and increase the risks of ventricular arrhythmias and sudden death. A retrospective cohort study has identified that the adjusted rate of sudden death from cardiac causes is 5 times as high in patients concurrently using CYP3A inhibitors and erythromycin compared with patients who used neither CYP3A inhibitors nor erythromycin. Clarithromycin has a lower affinity for the CYP3A4 isozyme than other macrolides but is still involved in drug interactions involving the CYP450 system. Azithromycin has virtually no effect on hepatic metabolism and does not alter the PK properties of other drugs. The effects of oral anticoagulants may be increased with clarithromycin and erythromycin. Clarithromycin and azithromycin share the macrolide class’s ability to alter gastrointestinal flora, which has been implicated in a drug interaction with digoxin resulting in enhancement of the oral bioavailability of digoxin. More recent data suggests that the macrolide clarithromycin inhibits the P-glycoprotein–mediated tubular secretion of digoxin and this mechanism is responsible for the increase in serum digoxin concentrations observed when these 2 agents are administered concurrently. Due to the potential for QT interval prolongation, Torsades de Pointes, or ventricular arrhythmias, coadministration of cisapride (only available in the United States via an investigational limited access program) with either erythromycin or clarithromycin is contraindicated.

**FLUOROQUINOLONES**

Fluoroquinolones undergo significant drug interactions with divalent and trivalent cations, as found in antacids, calcium supplements, didanosine, sucralfate,

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**Table 4. Antimicrobial Activity of Telithromycin Against Common Respiratory Pathogens**

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC₉₀ mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae (n = 10 103)</td>
<td>0.5</td>
</tr>
<tr>
<td>Haemophilus influenzae (n = 2706)</td>
<td>4</td>
</tr>
<tr>
<td>Streptococcus pyogenes (n = 3918)</td>
<td>0.03</td>
</tr>
<tr>
<td>Moraxella catarrhalis (n = 2314)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae (n = 25)</td>
<td>&lt;0.015</td>
</tr>
<tr>
<td>Chlamydia pneumoniae (n = 19)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

MIC₉₀ = minimum inhibitory concentration at which 90% of isolates are inhibited; n = number of isolates tested.

Data from Doern and Brown, Kasbekar and Acharya, Zhanel et al, Bebear et al, Roblin and Hammerschlag.
or enteral nutritional products, resulting in a decrease in the absorption and bioavailability of the antibiotic. This drug interaction is mediated through chelation of metal cations with the fluoroquinolone and the resulting formation of insoluble drug-cationic complexes. Levofloxacin has been associated with elevations of the prothrombin time and International Normalized Ratio when used with warfarin.

Ciprofloxacin has also been reported to decrease the metabolism of warfarin, primarily in elderly patients. The metabolism of theophylline, which is primarily via the CYP1A2 isozyme, is inhibited by ciprofloxacin resulting in increases in theophylline concentrations. Another important drug interaction has been recently described with ciprofloxacin. The bioavailability of ciprofloxacin has been reported to be decreased by 48% in healthy subjects who received concomitant sevelamer hydrochloride (2.8 g).

**KETOLIDES**

Approximately half of the metabolism of telithromycin is by CYP3A4 and the remaining 50% is via CYP450-independent mechanisms. Because telithromycin is a derivative of the macrolide class, it would be reasonable to assume that ketolides will share some of the same drug interactions. However, telithromycin does not form a nitrosalkane complex with CYP, unlike macrolides (eg, erythromycin and clarithromycin), and is therefore theoretically less likely to result in macrolide-class drug interactions. In clinical practice however, telithromycin can have a significant inhibitory effect on the metabolism of CYP3A4 substrates resulting in increased concentrations of the other agent. The lipophilic statins, such as atorvastatin, lovastatin, and simvastatin, are examples of substrates of the CYP3A4 isozyme. Concomitant administration of telithromycin and these lipophilic statins is associated with a decrease in the metabolism of the statin. Telithromycin concentrations are minimally affected by the CYP3A4-inhibiting drugs itraconazole and ketoconazole. Telithromycin plasma concentrations were found to increase when administered concomitantly with ketoconazole due to ketoconazole-mediated inhibition of CYP3A4 in a study of subjects aged 60 years and older with renal impairment. This drug interaction between telithromycin and ketoconazole did not induce any clinically significant prolongations in the QTc interval. Due to the potential for increased plasma concentration of cisapride and cardiac arrhythmias or QTc interval prolongation, telithromycin is contraindicated with cisapride.

**SAFETY PROFILE OF ANTIBIOTICS**

**BETA-LACTAMS**

The beta-lactam antibiotics are generally well tolerated but have been associated with gastrointestinal intolerance in clinical study. Immunoallergic reactions can also occur in patients taking beta-lactam antibiotics. The mechanism behind these allergic reactions has been studied and is thought to be linked to the antigenic determinants carried by the beta-lactam ring or by the side chain on the ring. This relationship between hypersensitivity reactions and chemical structure provides the rationale for cross-sensitivity that has been observed between the penicillins and cephalosporins.

**MACROLIDES**

Macrolide antibiotics have been reported to be one of the safest classes of antibacterials currently available. Dose-related gastrointestinal intolerance is the most frequent side effect associated with exposure to macrolides use. However, a much more serious event has been linked to these antibiotics. The rate of sudden death from cardiac causes has been reported to be twice as high in patients currently taking erythromycin compared with patients who previously or never used erythromycin. It should be noted that this cardiac toxicity was even more pronounced in patients who were taking a concomitant agent known to inhibit CYP3A.

**FLUOROQUINOLONES**

This class of drugs has been used in large populations of patients; therefore, a large amount of safety data has been generated with the fluoroquinolones. Phototoxicity was a commonly encountered side effect of fluoroquinolone exposure but the newer fluoroquinolones are not associated with this event to the same extent as older agents in this class. Fluoroquinolone-induced photosensitivity usually presents as erythema, edema, desquamation, and hyperpigmentation and can include painful blistering. The side effect appears to be dose related and quickly
resolves within a few weeks upon discontinuation of fluoroquinolone therapy. QTc interval prolongation is a class effect of all fluoroquinolones. The severity of this cardiovascular effect can range from asymptomatic increases in the QTc interval to ventricular fibrillation and sudden cardiac death. Fluoroquinolones should be closely monitored or avoided in patients with significant cardiovascular disease, history of arrhythmia, or are receiving drugs that prolong the QTc interval or inhibit the metabolism of QTc-prolonging drugs. As a class, fluoroquinolones have been associated with hypo- or hyperglycemia as a side effect.

Gatifloxacin, temafloxacin, and to a lesser extent levofloxacin have been found to stimulate insulin secretion by inhibiting pancreatic beta-cell K+ (adenosine triphosphate) channels resulting in hypo-glycemia. Additionally, ciprofloxacin and levofloxacin have displayed some risk for causing central nervous system adverse effects such as dizziness and headaches. Tendon rupture has also been associated with fluoroquinolone use, and the risk of tendon rupture appears to be increased in patients with renal disease or concurrent corticosteroid use.

Ketolides

The most frequently reported adverse events in the telithromycin clinical studies of more than 4700 patients included diarrhea, nausea, headache, dizziness, vomiting, loose stools, dysgeusia, and dyspepsia. Telithromycin has the potential to prolong QTc interval; however, the clinical significance of this finding is not fully understood. The incidence of treatment-emergent visual adverse events in controlled phase 3 studies of telithromycin was 1.1%. Visual symptoms included an effect on visual accommodation resulting in blurred vision, difficulty focusing, and diplopia. In clinical studies, women and patients younger than 40 years of age experience a higher incidence of telithromycin-associated visual adverse events.

Correct Drug, Duration, and Dose

While it may seem more than obvious, it is important to reiterate that antibiotics are only indicated for treatment of bacterial infections. This common-sense approach is routinely ignored for a variety of reasons including pressures from patients and parents, constraints on the clinician's time, and lack of appreciation of the possible impact on resistance. The use of antibiotics for nonbacterial or self-limiting infections can have important consequences such as an increased risk of adverse reactions, the potential for drug interactions, and the development of resistant bacteria.

Although the antimicrobial agent used to treat RTIs must be active against the common pathogens that cause RTIs, bacterial eradication is the key to antibiotic therapy and drives optimal therapeutic outcome. In addition, antibiotic choices should reflect local resistance prevalence. These simple concepts should not be discounted given that the spontaneous clinical recovery, which is common in mild-to-moderate RTIs, may mask the differences in bacteriological effectiveness of antibiotics and allow for the continued use of suboptimal agents. As previously discussed, the PD properties of antimicrobials may provide the clinician with a means to differentiate the various antibiotics used for RTIs.

Drug Resistance Strategies

It is inevitable that antibiotic resistance will develop. However, efforts need to be made to slow and control this process as much as possible. Vaccination against S. pneumoniae is readily available and an important mechanism to fight resistance. The 23-valent pneumococcal polysaccharide vaccine and the 7-valent pneumococcal conjugate vaccine (PCV7) are highly effective in providing protection against the most commonly isolated pneumococcal serotypes. Use of vaccines will not prevent the development of resistant strains, but it may prevent invasive infection caused by a drug-resistant organism. PCV7 for children has been available since February 2000 and use has led to a decrease in the carriage rate of S. pneumoniae and the incidence of invasive pneumococcal disease, acute otitis media, and pneumonia in vaccinated patients. Use of the vaccine has resulted in H. influenzae emerging as the most common bacterial pathogen in otitis media in vaccinated children. In addition, use of the conjugate vaccine has been shown to be effective for preventing infections caused by drug-resistant strains. This is evidenced by 35% fewer infections occurring due to penicillin-non-susceptible strains in 2001 compared with 1999.

When treating RTIs, antimicrobials with chemical properties that may reduce the risk of developing resistance should be considered. Such factors that may influence resistance include potency, half-life, bactericidal activity, and binding affinity at multiple sites. Another aspect of antimicrobial therapy to consider is the prevention of “collateral damage.” Collateral damage has been defined as, “a term used to refer to
ecological adverse effects of antibiotic therapy; namely, the selection of drug-resistant organisms and the unwanted development of colonization or infection with multidrug-resistant organisms." Thus, antibiotics with a tailored spectrum of activity for pathogens commonly encountered in RTIs but without broad-spectrum coverage for normal flora can improve RTI treatment outcomes while avoiding collateral damage. Telithromycin is an example of an antimicrobial with a spectrum of activity tailored for RTIs.

**CONCLUSIONS**

By optimizing PK/PD properties of antimicrobial agents, the most appropriate dose and duration of therapy for the management of RTIs can be determined. However, the unnecessary use of antibiotics should be avoided. Pharmacists should be encouraged to take an active role in the judicious use of antimicrobial therapy for RTIs, including the use of no antibiotic in cases of viral or self-limiting infection. Part of this approach should be the promotion of the appropriate use of antibacterial therapy for RTIs when interacting with patients or other clinicians. In addition, pharmacists should educate patients about adhering to their treatment regimens and counsel them on potential side effects and drug interactions. When antimicrobial therapy is warranted, treatment should be individualized taking into account concomitant medications and the medical history of the patient. Appropriate pharmaceutical management of bacterial RTIs is a valuable tool at the pharmacist's disposal for the slowing down of the inevitable development of bacterial resistance.

**REFERENCES**


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