Erythromycin, the first macrolide antibiotic discovered, has been used since the early 1950s for the treatment of upper respiratory tract and skin and soft tissue infections caused by susceptible organisms, especially in patients who are allergic to penicillin. Several drawbacks, however, have limited the use of erythromycin, including frequent gastrointestinal intolerance and a short serum half-life. Advanced macrolide antimicrobials synthesized by altering the erythromycin base have resulted in compounds with broader activity, more favorable pharmacokinetics and pharmacodynamics, and better tolerability. In 1991 and 1992, the US Food and Drug Administration (FDA) approved two of these agents, clarithromycin (Biaxin) and azithromycin (Zithromax), for clinical use. Since their introduction, these advanced macrolides have been used extensively for the treatment of respiratory tract infections, sexually transmitted diseases, and infections caused by *Helicobacter pylori* and *Mycobacterium avium* complex (MAC).

Ketolides, a new class of macrolides, share many of the characteristics of the advanced macrolides. Their in vitro spectrum of activity also includes gram-positive organisms (*Streptococcus pneumoniae, Streptococcus pyogenes*) that are macrolide-resistant.
resistant. Telithromycin (Ketek), specifically developed for the treatment of respiratory tract infections, received FDA approval in 2004. In 2007, because of increasing reports of hepatotoxicity, the FDA withdrew two of telithromycin’s treatment indications, limiting its approval to the treatment of mild to moderate community-acquired pneumonia.

Glycylcyclines are a new class of antimicrobial agents developed to overcome tetracycline-specific resistance mechanisms (efflux pumps and ribosomal protection). Tigecycline (Tygacil), a derivative of minocycline, is the first antimicrobial in this class to receive FDA approval. Tigecycline is active in vitro against a broad spectrum of bacteria, including multidrug-resistant (MDR) organisms, and is indicated for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections and community-acquired pneumonia. This article reviews the pharmacokinetics, antimicrobial activity, clinical use, and adverse effects of these antimicrobial agents.

**CHEMISTRY**

Erythromycin is a macrolide antibiotic whose structure consists of a macrocyclic 14-membered lactone ring attached to two sugar moieties (a neutral sugar, cladinose, and an amino sugar, desosamine). In the acidic environment of the stomach, it is rapidly degraded to the 8,9-anhydro-6,9-hemiketal and then to the 6,9,9,12-spiroketal form. The hemiketal intermediate may be responsible for the gastrointestinal adverse effects associated with erythromycin.1

Clarithromycin (6-O-methylerythromycin) is synthesized by substituting a methoxy group for the C-6 hydroxyl group of erythromycin. This substitution creates a more acid-stable antimicrobial and prevents the degradation of the erythromycin base to the hemiketal intermediate, which results in improved oral bioavailability and reduced gastrointestinal intolerance.2 Clarithromycin is available as immediate-release tablets (250 or 500 mg), extended-release tablets (500 mg), and granules for oral suspension (125 or 250 mg/5 mL).

Azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) is formed by inserting a methyl-substituted nitrogen in place of the carbonyl group at the 9a position of the aglycone ring. The resulting dibasic 15-membered ring macrolide derivative is more appropriately referred to as an azalide. This change produces a compound that is more acid stable and has a longer serum half-life (t1/2), increased tissue penetration, and greater activity against gram-negative organisms compared with erythromycin.2 Azithromycin is available as 250- or 500-mg immediate-release tablets, 2-g microsphere extended-release powder, oral suspension (100–200 mg/5 mL), and intravenous preparation (lyophilized 500 mg/10 mL vial).

Ketolides are synthesized by two changes in the 14-membered erythronolide A ring: substituting a keto function for the alpha-L-cladinose moiety at position 3 and replacing the hydroxyl group at position 6 with a methoxy group.3 These changes promote greater acid stability and prevent induction of macrolide-lincosamide-streptogramin B (MLSB) resistance.4 Telithromycin is synthesized by cycling of the C11-12 positions to form a carbamate ring with an imidazo-pyridyl group attachment that enhances binding to the bacterial ribosome and in vitro activity.5 Telithromycin is available in 300- or 400-mg tablets.

Tigecycline is synthesized by the addition of a tert-butyl-glycylamido group to the C-9 position of minocycline. This addition overcomes the efflux pump and ribosomal protection mechanisms that confer resistance to tetracycline and extends its antimicrobial activity against a variety of bacteria.6 Tigecycline is only available as an intravenous preparation (lyophilized 50 mg/vial).
MECHANISM OF ACTION AND RESISTANCE

The macrolides and ketolides are bacteriostatic antimicrobials. They reversibly bind to domain V of 23S ribosomal RNA (rRNA) of the 50s subunit of the bacterial ribosome inhibiting RNA-dependent protein synthesis. The ketolides bind with a 10- to 100-fold higher affinity to the ribosome than erythromycin. The ketolides also have a greater affinity for binding to domain II of the 23S rRNA, which enables it to maintain antimicrobial activity against bacterial strains that are macrolide resistant because of alterations in the domain V binding site.

Macrolide resistance in streptococci arises from either an alteration of the drug-binding site on the ribosome by methylation (MLS\(_B\) resistance) or by active drug efflux. The efflux mechanism is mediated by the macrolide efflux (\textit{mef}) genes and is specific for 14- and 15-membered macrolides. Macrolide resistance is usually low level (minimum inhibitory concentrations [MICs] 1–32 mg/L), and in vitro susceptibility to ketolides, lincosamides, and streptogramins is maintained. Methylation of an adenine residue in domain V of the 23S rRNA, mediated by the erythromycin ribosome methylase (\textit{erm}) genes, prevents binding of the macrolides and ketolides to domain V and results in high level macrolide resistance (MIC \(\geq\) 64 mg/L). Ketolides presumably maintain their antimicrobial activity by virtue of their ability to bind to an alternative site—domain II of the 23S rRNA. Methylation may be either induced or constitutively expressed, and resistance to erythromycin implies cross-resistance to clarithromycin and azithromycin. Clarithromycin and azithromycin can induce methylase production but telithromycin does not. Decreased susceptibility to telithromycin in streptococci has been associated with a variety of mutations in the \textit{erm}(B) gene and its promoter region, ribosomal proteins L4 and L22, and in the 23S rRNA.

Tigecycline is also a bacteriostatic antibiotic. It reversibly binds to the 30S ribosomal subunit inhibiting protein synthesis. Glycylcyclines bind with a fivefold higher affinity to the ribosome compared with tetracyclines. This enhanced ribosomal binding enables tigecycline to overcome resistance caused by ribosomal protection. Tigecycline also maintains activity against bacteria-containing tetracycline-specific efflux pumps by failing to be recognized as a substrate. Susceptibility to tigecycline is reduced, however, by the overexpression of multidrug efflux pumps (eg, MexXY, AcrAB) that may be found in gram-negative organisms. These multidrug efflux pumps are naturally expressed in \textit{Pseudomonas aeruginosa}. Reduced susceptibility of \textit{Acinetobacter} \textit{spp} to tigecycline has been reported in isolates with a resistance-nodulation-division-type multicomponent efflux transporter.

PHARMACOKINETICS

The structural alterations to the erythromycin base used to synthesize the advanced macrolides and ketolides result in improved pharmacokinetic properties. Compared with erythromycin, clarithromycin and azithromycin are more acid stable and have greater oral bioavailability (55% and 37%, respectively). The peak plasma concentration of clarithromycin immediate-release tablets is increased by 24% when administered with food, but the overall bioavailability is unchanged. The bioavailability of the extended-release formulation, however, is decreased by 30% when administered in the fasting state and should be administered with food. The bioavailabilities of the tablet, sachet, or suspension formulations of azithromycin are not affected by meals. The absorption of azithromycin 2-g extended-release microsphere formulation is increased with food and should be administered on an empty stomach to ensure appropriate (slower) absorption from the gastrointestinal tract. Oral absorption of an 800-mg dose of telithromycin is excellent (90%); however, 33% of the dose undergoes
first-pass metabolism, which results in an absolute oral bioavailability of 57%.23 The bioavailability, rate, and extent of absorption of telithromycin are unaffected by food.24

The single-dose pharmacokinetics of erythromycin, clarithromycin, azithromycin, and telithromycin are summarized in Table 1. Several differences between the pharmacokinetics of these antimicrobials are apparent. First, the peak serum concentration (C_{max}) of azithromycin after a 500-mg dose is fivefold lower than that achieved with a comparable dose of clarithromycin or telithromycin. Although azithromycin concentrations are low in the serum, tissue concentrations are significantly higher, as discussed later. Second, the terminal half-life of azithromycin and telithromycin are long enough to allow once-daily dosing. Twice-daily dosing of the immediate-release formulation of clarithromycin is necessary based on the terminal half-life of 4 to 5 hours.2 Protein binding is higher for clarithromycin and telithromycin (60%–70%) compared with azithromycin (7%–50%).

Clarithromycin is metabolized to an active metabolite, 14-hydroxyclarithromycin. Larger doses of clarithromycin result in nonlinear increases in the t_{1/2} and in the area under the plasma concentration-time curve (AUC) of clarithromycin because of saturation of the metabolic pathway.25 Steady-state peak plasma concentrations of 3 to 4 mg/L are achieved within 3 days with clarithromycin, 500 mg, every 8 to 12 hours and the elimination half-life increases to 5 to 7 hours.19 Although steady-state peak plasma concentrations are lower and achieved later with the extended-release formulation of clarithromycin than a comparable daily dose of the immediate-release formulations, the 24-hour AUC is equivalent between the two formulations, supporting the once-daily dosing of the extended-release formulation.20

The azithromycin 2-g extended-release microsphere formulation has a slower rate of absorption compared with an equivalent dose of the immediate-release tablet, which results in a mean peak serum concentration that is 57% lower and a t_{max} that is 2.5 hours later.22 The mean relative bioavailability of the extended-release form was 82.8%. When compared with a 3-day regimen of 500-mg azithromycin immediate-release tablets in healthy subjects, a 2-g single dose of extended-release azithromycin on day 1 had a C_{max} and 24-hour AUC that were two- and threefold higher, respectively. Overall AUC for the 5-day study period was equivalent for the two dosing regimens.26 Daily doses of telithromycin, 800 mg, result in a steady-state peak plasma concentration of 2.27 mg/L and a terminal half-life of 9.81 hours.27

Tigecycline is only available in an injectable formulation. The recommended dosage is an initial load of 100 mg, followed by a maintenance dose of 50 mg every 12 hours.

### Table 1
Comparative pharmacokinetics of macrolide antibiotics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Erythromycin Base</th>
<th>Azithromycin</th>
<th>Clarithromycin</th>
<th>14-Hydroxy-Clarithromycin</th>
<th>Telithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability %</td>
<td>25</td>
<td>37</td>
<td>55</td>
<td>35</td>
<td>57</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>0.3–0.9</td>
<td>0.4</td>
<td>2.1–2.4</td>
<td>0.6</td>
<td>1.9–2.0</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>3–4</td>
<td>2</td>
<td>2</td>
<td>2–3</td>
<td>1.0</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>2–3</td>
<td>40–68</td>
<td>3–5</td>
<td>4–7</td>
<td>7.16–13</td>
</tr>
<tr>
<td>AUC (mg/L × h)</td>
<td>8</td>
<td>3.4</td>
<td>19</td>
<td>5.7</td>
<td>7.9–8.25</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under plasma concentration time curve; C_{max}, peak serum concentration; t_{max}, time to peak serum concentration; t_{1/2}, serum half-life.

* Mean values after a single 500-mg oral dose (800-mg dose for telithromycin).

infused over 30 to 60 minutes. Pooled data from healthy volunteers showed that the C\text{max} after a single 100-mg dose was 1.45 mg/L and 0.90 mg/L after 30- and 60-minute infusions, respectively. The C\text{max} at steady state was 0.87 mg/L and 0.63 mg/L after 30- and 60-minute infusions, respectively, and the 24-hour AUC was 4.70 mg/L × h.

The serum half-life was 27.1 hours after a single 100-mg dose and increased to 42.2 hours with multiple doses of 50 mg twice daily. The pharmacokinetics of tigecycline are not affected by the presence of food or differences in sex or age.28–30

The macrolides and ketolides are lipophilic and are extensively distributed in body fluids and tissues. Mean tissue concentrations are 2- to 20-fold greater than serum concentrations for clarithromycin and are 10- to 100-fold greater than serum concentrations for azithromycin.31,32 Tissue concentrations do not peak until 48 hours after administration of azithromycin and persist for several days afterwards.2 Twenty-four hours after the last dose of drug administration, concentrations of clarithromycin and azithromycin in lung epithelial cell lining fluid exceeded serum concentrations by 20-fold.33 Measurements at this interval also revealed that alveolar macrophage concentrations were 400 times (clarithromycin) and 800 times (azithromycin) greater than their respective serum concentrations. Telithromycin also has excellent penetration into bronchopulmonary tissues. Levels in alveolar macrophages (median concentration 81 mg/L) significantly exceeded plasma levels 8 hours after dosing and maintained elevated levels 24 and 48 hours after dosing (23 mg/L and 2.15 mg/L, respectively).34 Concentrations of telithromycin in bronchial mucosa and epithelial lining fluid exceeded for 24 hours the mean MIC\textsubscript{90} of \textit{S pneumoniae}, \textit{Moraxella catarrhalis}, and \textit{Mycoplasma pneumoniae}.35 In these studies, 24 hours after the last dose of drug administration, concentrations of telithromycin in lung epithelial cell lining fluid were 12-fold, and in alveolar macrophages the levels were 400-fold greater than their respective serum concentrations.

Tigecycline is also distributed widely in tissues, with a steady-state volume of distribution of 7 to 10 L/kg.30 At steady-state levels, the tigecycline AUC\textsubscript{0–12h} in alveolar cells and epithelial lining fluid was 78-fold higher and 32% higher compared with serum.36 Tissue levels of tigecycline were higher in the gallbladder (38-fold), lung (8.6-fold), and colon (2.1-fold) compared with serum levels 4 hours after a single 100-mg dose. Synovial fluid and bone concentrations, however, were 0.58 and 0.35 lower, respectively, relative to serum.37 Tissue penetration of tigecycline into skin blister fluid was 74% of serum concentration.38

Clarithromycin is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzymes to the active 14-hydroxy form and six additional products. Thirty percent to 40% of an oral dose of clarithromycin is excreted in the urine either unchanged or as the active 14-hydroxy metabolite.39 The remainder is excreted into the bile. In patients with moderate to severe renal impairment (ie, creatinine clearance < 30 mL/min), the dose should be reduced.39 In patients with moderate to severe hepatic impairment and normal renal function, there is less metabolism of clarithromycin to the 14-hydroxy form, which results in decreased peak plasma concentrations of the metabolite and increased renal excretion of unchanged clarithromycin. Dosing modifications do not seem to be necessary for these patients.40

Azithromycin elimination occurs primarily in the feces as the unchanged drug, and urinary excretion is minimal.41 Unlike clarithromycin, azithromycin does not interact with the cytochrome P450 system.42 In patients with mild or moderate hepatic impairment, dosing modifications do not seem to be necessary.42,43

Telithromycin is eliminated via multiple pathways, including unchanged drug in feces (7%) and urine (13%) and the remainder via hepatic metabolism by the CYP 3A4 and 1A isoenzymes.44 Four metabolites of telithromycin do not have appreciable
antibacterial activity. Plasma concentrations and AUC were 1.4- and 1.9-fold higher in patients with creatinine clearance less than 30 mL/min. In patients with mild to moderate renal impairment, there was no significant change in the pharmacokinetics of telithromycin. Dosing modifications are not necessary when administering telithromycin to patients with hepatic impairment because pharmacokinetics do not change significantly as the result of a compensatory increase in renal excretion.

Tigecycline is not extensively metabolized and is primarily eliminated unchanged via biliary excretion. In healthy male volunteers who received 14C-tigecycline, 59% of the radioactive dose was recovered in the feces and 33% recovered in the urine. Secondary elimination pathways include renal excretion of unchanged drug and, to a lesser degree, metabolism to glucuronide conjugates and N-acetyl-9-aminomycinoline. Dose adjustment is not necessary based on age, sex, renal impairment, or mild to moderate hepatic impairment (Child Pugh class A-B). In patients with severe hepatic impairment (Child Pugh class C), the maintenance dose should be reduced by 50%.

SPECTRUM OF ACTIVITY

The Clinical and Laboratory Standards Institute provides guidelines for the interpretation of in vitro MICs for clarithromycin, azithromycin, and telithromycin. The FDA established breakpoints for tigecycline (Table 2). The breakpoints for azithromycin are based on expected tissue concentrations, whereas the breakpoints for clarithromycin are based on achievable serum concentrations. In vitro susceptibility testing does not account for the antimicrobial activity of the active 14-hydroxy metabolite and may underestimate the activity of clarithromycin. In vitro MIC measurements also do not account for the pharmacodynamic properties of an antimicrobial (eg, tissue penetration, intracellular half-life, postantibiotic effect) and may not predict its relative efficacy at the site of infection.

Comparative in vitro susceptibility data for erythromycin, clarithromycin, azithromycin, and telithromycin are shown in Table 3. Compared with erythromycin, clarithromycin demonstrates equal or better in vitro activity against gram-positive organisms, whereas azithromycin is two- to fourfold less active. Azithromycin and clarithromycin are generally inactive against methicillin-resistant staphylococci. Telithromycin is more active in vitro against S pneumoniae compared with clarithromycin.

### Table 2

<table>
<thead>
<tr>
<th>Susceptibility test result interpretative criteria</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
<th>Telithromycin</th>
<th>Tigecycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>$\leq 2$</td>
<td>$\geq 8$</td>
<td>$\leq 2$</td>
<td>$\geq 8$</td>
</tr>
<tr>
<td>Streptococcus spp, including pneumoniae</td>
<td>$\leq 0.25$</td>
<td>$\geq 1$</td>
<td>$\leq 0.5$</td>
<td>$\geq 2$</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Haemophilus spp</td>
<td>$\leq 8$</td>
<td>$\geq 32$</td>
<td>$\leq 4$</td>
<td>NA</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Values expressed as MIC (mg/L).

Data from Tygacil (tigecycline) prescribing information. 2008;2008(11/28); Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility Testing; Eighteenth Informational Supplement; 2008.
Table 3
Comparative in vitro activities of macrolide/ketolide antibiotics*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Erythromycin</th>
<th>Azithromycin</th>
<th>Clarithromycin</th>
<th>Telithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive aerobes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythromycin susceptible</td>
<td>0.06–0.12</td>
<td>0.12–0.25</td>
<td>0.06–0.12</td>
<td>0.03</td>
</tr>
<tr>
<td>ermA resistance</td>
<td>1–32</td>
<td>16–32</td>
<td>2–16</td>
<td>0.015–0.25</td>
</tr>
<tr>
<td>ermB resistance</td>
<td>&gt; 64</td>
<td>&gt; 64</td>
<td>&gt; 64</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>mefA resistance</td>
<td>8–16</td>
<td>8</td>
<td>8–16</td>
<td>0.25–1</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythromycin sensitive</td>
<td>0.03–0.12</td>
<td>0.06–0.25</td>
<td>0.03–0.12</td>
<td>0.008–0.03</td>
</tr>
<tr>
<td>erythromycin resistant ermB</td>
<td>≥ 32</td>
<td>≥ 64</td>
<td>≥ 64</td>
<td>0.125–0.5</td>
</tr>
<tr>
<td>erythromycin resistant mefA</td>
<td>8–16</td>
<td>8–16</td>
<td>8</td>
<td>0.25–1</td>
</tr>
<tr>
<td><strong>Gram-negative aerobes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>8</td>
<td>2–4</td>
<td>4–16</td>
<td>2–4</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>0.125–0.25</td>
<td>0.06–0.12</td>
<td>0.12–0.25</td>
<td>0.12</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>0.12–2</td>
<td>0.25–2</td>
<td>0.06–0.25</td>
<td>0.015–0.06</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>0.5</td>
<td>0.25</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Other pathogens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>0.06–0.25</td>
<td>0.125–0.25</td>
<td>0.03–0.06</td>
<td>0.06–0.25</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>≤ 0.015–0.06</td>
<td>≤ 0.015</td>
<td>≤ 0.015–0.03</td>
<td>≤ 0.015</td>
</tr>
</tbody>
</table>

* Values expressed as MIC 90 (mg/L). Ranges indicate the different values reported in references. Data from references.3,44,50–52

and azithromycin and maintains activity against strains that are macrolide resistant.54 In one study, the MIC90 for telithromycin against *S pneumoniae* strains with the mefA gene was 0.25 mg/L or less, compared with 1 to 4 mg/L for macrolides. Against strains expressing the ermB gene, telithromycin had an MIC90 of 0.5 mg/L, whereas the macrolides had an MIC90 of more than 64 mg/L.55 Telithromycin MIC90 increased from 0.015 mg/L to 0.25 mg/L and 0.5 mg/L for penicillin-intermediate and penicillin-resistant pneumococcal strains, respectively.56 Telithromycin is also two- to eightfold more active against erythromycin-susceptible strains of *S aureus* compared with clarithromycin and azithromycin. Telithromycin maintains activity against macrolide-resistant strains of *S aureus* that have an inducible MLSB gene but not against strains in which resistance is constitutively expressed.57

The newer macrolides demonstrate enhanced activity against respiratory pathogens. The MIC against *H influenzae* for clarithromycin, combined with its active metabolite, 14-hydroxylarithromycin, is two- to fourfold lower compared with erythromycin.58 Azithromycin and telithromycin are more active against *H influenzae* with an MIC four- to eightfold lower compared with erythromycin.59 Clarithromycin seems more active in vitro than azithromycin and erythromycin against *Legionella pneumophila* and *Chlamydia pneumoniae*, whereas azithromycin demonstrates better activity against *M catarrhalis* and *M pneumoniae*.53,60 Telithromycin has excellent in vitro activity against *Mycoplasma, Chlamydia*, and *Legionella* and is more active compared with the macrolides.44

Azithromycin has activity against enteric pathogens, including *Escherichia coli*, *Salmonella* spp, *Yersinia enterocolitica*, and *Shigella* spp.53 Clarithromycin and telithromycin have no in vitro activity against these gram-negative organisms.
Azithromycin is more active against *Campylobacter jejuni* than erythromycin or clarithromycin, whereas clarithromycin has greater activity against *H pylori*.61,62

Azithromycin and clarithromycin have similar or increased in vitro activity against genital pathogens compared with erythromycin. *Neisseria gonorrhoeae, Haemophilus ducreyi,* and *Ureaplasma urealyticum* are susceptible to both antibiotics, with azithromycin demonstrating lower MICs.61,62 Clarithromycin is approximately tenfold more active than erythromycin against *Chlamydia trachomatis*, whereas azithromycin’s activity is similar to that of erythromycin.61,62 Only azithromycin demonstrated in vitro activity against *Mycoplasma hominis*.49

Tigecycline has a broad spectrum of activity against aerobic and anaerobic gram-positive and -negative pathogens, including micro-organisms that demonstrate resistance to multiple classes of antimicrobials. In addition to the Clinical and Laboratory Standards Institute breakpoints listed in Table 2, the MICs indicating susceptibility to tigecycline are 0.25 mg/L or less for vancomycin-susceptible *Enterococcus faecalis*, 2 mg/L or less for *Enterobacteriaceae* and 4 mg/L or less for anaerobes. *P aeruginosa* isolates are intrinsically resistant to tigecycline. Tigecycline also has limited activity against *Proteus* spp and *Providencia* spp.63

The Tigecycline Evaluation and Surveillance Trial evaluated the in vitro activity of tigecycline against a large population of organisms.64,65 Overall, the global in vitro susceptibility data showed that tigecycline was highly active against most gram-positive isolates, including 100% of the methicillin-susceptible *S aureus*, 99% of the methicillin-resistant *S aureus*, and 98% of the vancomycin-resistant enterococcus isolates tested. Ninety-five percent of *Enterobacteriaceae* were susceptible to tigecycline at the FDA susceptibility breakpoint of 2 mg/L or less. Tigecycline maintained in vitro activity against MDR gram-negative organisms, including *E coli* and *Klebsiella* spp isolates expressing extended-spectrum β-lactamas and carbapenemase-producing strains of *Enterobacteriaceae*.66 Tigecycline demonstrated excellent activity against *Acinetobacter baumanii* with MIC 50/90 results of 0.5/2 mg/L.67,68 Tigecycline also was active against community-acquired infectious agents such as *S pneumoniae* and *H influenzae* regardless of penicillin susceptibility or β-lactamase production, with MIC 90 values of less than 0.5 mg/L.69,70

**CLINICAL USE: MACROLIDES AND KETOLIDES**

**Respiratory Tract Infections**

**Upper respiratory tract infections**

Clarithromycin, azithromycin, and telithromycin are effective against the most frequently isolated bacterial causes of pharyngitis, otitis media, and sinusitis. A 5-day course of the extended-release formulation of clarithromycin, azithromycin, or telithromycin is equally as effective as a 10-day course of penicillin for the treatment of streptococcal pharyngitis.2,71,72 In comparative trials, clarithromycin has proved to be equivalent to amoxicillin, amoxicillin-clavulanate, and cefaclor for the treatment of acute otitis media in children.73,74 Otitis media in children was also treated equally well with azithromycin (3 or 5 days) versus 10 days of amoxicillin/clavulanate or cefaclor or 5 days of cefdinir.75,76 One study showed greater efficacy with a 10-day course of high-dose amoxicillin/clavulanate compared with a 5-day course of azithromycin.77 A single oral dose of azithromycin at 30 mg/kg was as effective as a 10-day course of high-dose amoxicillin.78

For the treatment of acute sinusitis, clarithromycin had equivalent efficacy compared with cefuroxime axetil, levofloxacin, or ciprofloxacin.79–81 Once-daily dosing of the extended-release formulation of clarithromycin was comparable to amoxicillin/clavulanate in the treatment of acute maxillary sinusitis.82 Studies for acute sinusitis treatment
with azithromycin concluded that a 3-day regimen (500 mg daily) was equally efficacious as a 10-day course of amoxicillin-clavulanate, and a single dose of the 2-g azithromycin extended-release microsphere formulation had a similar cure rate as a 10-day course of levofloxacin. A 5-day course of telithromycin was equally effective as a 10-day course of high-dose amoxicillin-clavulanate, cefuroxime axetil, or moxifloxacin. 

Currently, clarithromycin is approved for the treatment of pharyngitis caused by S pyogenes; the recommended dose is 250 mg every 12 hours for 10 days. Dosage for treatment of acute maxillary sinusitis is either 500 mg every 12 hours with the immediate-release tablets for 14 days or 2 × 500 mg every 24 hours with the extended-release tablets for 7 days. For children, the recommended dose is 7.5 mg/kg every 12 hours. Azithromycin is approved as a second-line agent for the treatment of pharyngitis. The recommended adult dose is 500 mg on the first day followed by 250 mg once daily on days 2 through 5. For children, the following azithromycin dosing regimens can be used for the treatment of otitis media: 30 mg/kg as a single dose, 10 mg/kg once daily for 3 days, or 10 mg/kg on the first day followed by 5 mg/kg on days 2 through 5. Azithromycin is also approved for the treatment of acute bacterial sinusitis; the adult dose is either 500 mg daily for 3 days or a single 2-g dose of the extended-release formulation and for children it is 10 mg/kg once daily for 3 days. Telithromycin is not FDA approved for the treatment of upper respiratory tract infections.

### Lower respiratory tract infections

Various trials have demonstrated the efficacy of clarithromycin, azithromycin, and telithromycin for treatment of lower respiratory tract infections, including acute bronchitis, acute exacerbation of chronic bronchitis (AECB), and community-acquired pneumonia. Most studies involved patients who were not hospitalized. Studies have shown equal efficacy of clarithromycin compared with ceftibuten, cefaclor, cefuroxime axetil, and cefixime for the treatment of lower respiratory tract infections. Comparable efficacy was also demonstrated between the once-daily dosing of the extended-release formulation of clarithromycin and the twice-daily dosing of the immediate-release formulation for the treatment of lower respiratory tract infections. Clinical cure rates for the treatment of AECB were similar between a 10-day course of clarithromycin compared with levofloxacin or cefuroxime axetil and a 5- or 7-day course of extended-release tablets of clarithromycin compared with telithromycin or amoxicillin/clavulanic acid. In a comparative trial between 5 days of gemifloxacin and 7 days of clarithromycin, clinical and bacteriologic cures were similar, but significantly more patients in the gemifloxacin group remained free of AECB recurrences. For the outpatient treatment of community-acquired pneumonia, equivalent efficacy has been shown between (1) clarithromycin 500 mg twice daily for 10 days and moxifloxacin or gatifloxacin and (2) clarithromycin extended-release tablets (2 × 500 mg tablets once daily for 7 days) and levofloxacin or trovafloxacin.

Azithromycin (500 mg on day 1 followed by 250 mg daily for 4 days) was equivalent to cefaclor in patients with outpatient community-acquired pneumonia. Outcomes for the treatment of community-acquired pneumonia were also similar between a 3-day course of azithromycin (1 g daily) and a 7-day course of amoxicillin-clavulanate. Two comparative trials showed that the efficacy of a single 2-g dose of azithromycin extended-release microsphere formulation was equivalent to a 7-day course of extended-release clarithromycin or levofloxacin for the treatment of mild to moderate community-acquired pneumonia in adults.

In an analysis of randomized controlled trials comparing azithromycin with alternative antimicrobials, azithromycin was found to have comparable clinical cure rates for the treatment of acute bronchitis and AECB and superior efficacy in the treatment of...
community-acquired pneumonia.\textsuperscript{104,105} For the treatment of AECB, azithromycin (500 mg daily for 3 days) was as efficacious as clarithromycin (500 mg twice daily for 10 days).\textsuperscript{106} Equivalent efficacy was also demonstrated between a 3- or 5-day course of azithromycin with either a 5-day course of moxifloxacin or a 7-day course of levofloxacin for the treatment of AECB.\textsuperscript{107,108} The clinical efficacy of telithromycin has been demonstrated in the outpatient treatment of community-acquired pneumonia in open-label studies and comparator trials. Telithromycin was equally effective when compared with a 10-day course of high-dose amoxicillin, twice-daily clarithromycin, or a 7- to 10-day course of trovafloxacin.\textsuperscript{109–111} Clinical cure rates and bacterial eradication were comparable in patients treated with either a 5- or 7-day course of telithromycin or a 10-day course of clarithromycin.\textsuperscript{112} Pooled analysis from clinical trials showed that telithromycin was effective in community-acquired pneumonia caused by erythromycin-resistant \textit{S pneumoniae} infections, including bacteremic patients.\textsuperscript{113,114} For the treatment of AECB, a 5-day course of telithromycin was equally effective as a 10-day course with cefuroxime axetil, clarithromycin, or amoxicillin-clavulanate.\textsuperscript{115,116} In several studies, however, eradication rates for \textit{H influenzae} were lower for telithromycin (66%) than comparators (88%).\textsuperscript{117}

Azithromycin and clarithromycin have been shown to be effective in the treatment of community-acquired pneumonia in patients who require hospitalization. Monotherapy with intravenous azithromycin was equally effective as a respiratory fluoroquinolone or a \(\beta\)-lactam plus macrolide regimen for patients hospitalized with community-acquired pneumonia.\textsuperscript{118–120} Recent comparative trials showed equivalent efficacy between respiratory fluoroquinolones and ceftriaxone plus azithromycin or clarithromycin in patients with community-acquired pneumonia who required hospitalization.\textsuperscript{121–123} Other studies imply an advantage in dual empiric therapy, including a macrolide, in reducing mortality in patients with community-acquired pneumonia or bacteremic pneumococcal pneumonia.\textsuperscript{124–126} Azithromycin monotherapy successfully treated 96% of patients (22/23) hospitalized with legionella pneumonia with a mean total duration of antibiotic therapy (intravenous plus oral) of 7.92 days.\textsuperscript{127} To date, limited data have been published on the use of telithromycin with a \(\beta\)-lactam antimicrobial for the treatment of community-acquired pneumonia in hospitalized patients.

Pneumococcal resistance to macrolides is prevalent. Surveillance studies in the United States revealed that 28% to 34% of \textit{S pneumoniae} isolates are macrolide resistant.\textsuperscript{128–130} Telithromycin resistance was infrequent in these studies. In the United States, 60% of the macrolide-resistant isolates exhibited low-level erythromycin resistance (16 mg/L) via expression of the \textit{mef(A)} gene, and nearly 20% expressed the \textit{mef(A)} gene and the \textit{erm(B)} gene, resulting in high-level resistance.\textsuperscript{131} The prevalence of macrolide resistance among \textit{S pneumoniae} isolates varies greatly among geographic regions, with the highest prevalence of resistance reported from Asia.\textsuperscript{132} Telithromycin resistance among \textit{S pneumoniae} isolates has been reported in a small number of case series. One surveillance study of \textit{S pneumoniae} isolates from Taiwan revealed that 2% were resistant to telithromycin and 96% were macrolide resistant.\textsuperscript{13,14,133,134}

Despite the high prevalence of macrolide resistance, reported clinical failures have been limited to small case series. In a prospective cohort study of patients who were discharged from emergency departments and prescribed clarithromycin for the treatment of community-acquired pneumonia, macrolide resistance among \textit{S pneumoniae} isolates did not affect outcomes.\textsuperscript{135} A matched-case control study of patients with bacteremic pneumococcal infections investigated whether development of breakthrough bacteremia during macrolide treatment was related to macrolide susceptibility of the isolate.\textsuperscript{136} Breakthrough bacteremia with an erythromycin-resistant
isolate occurred in 18 (24%) of 76 patients taking a macrolide, compared with none of the 136 matched patients with bacteremia with an erythromycin-susceptible isolate. Given the possibility of treatment failure, most guidelines recommend combining a macrolide with a β-lactam if risk factors are present for drug-resistant *S. pneumoniae*. Telithromycin maintains in vitro activity against macrolide-resistant isolates. Whether this translates into a therapeutic advantage in the empiric treatment of respiratory tract infections, especially when drug-resistant *S. pneumoniae* is of concern, needs to be determined.

Practice guidelines from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) provide recommendations for the empiric treatment of community-acquired pneumonia based on the clinical setting, presence of comorbidities, severity of disease, and risk for drug-resistant *S. pneumoniae*. Only treatment options that include a macrolide are discussed, and the reader is referred to the guidelines for alternative options. In the outpatient setting, recommended antimicrobial therapy for patients who were previously healthy and have no risk factors for drug-resistant *S. pneumoniae* includes any macrolide (erythromycin, azithromycin, clarithromycin). Recommended outpatient therapy for individuals who have comorbid conditions, have received antibiotics within the previous 3 months, or have other risk factors for drug-resistant *S. pneumoniae* includes a macrolide in combination with a β-lactam. The IDSA/ATS guidelines suggest that in regions in which high-level (MIC ≥ 16 mg/L) macrolide resistance among *S. pneumoniae* exceeds 25%, alternative antimicrobials should be considered in lieu of the macrolides. For patients who require hospitalization, a macrolide combined with a β-lactam is one of the preferred regimens recommended. Azithromycin monotherapy is not endorsed as a routine treatment option. The use of telithromycin is not addressed in the practice guidelines because at the time of publication, telithromycin’s safety profile was being re-evaluated by the FDA.

The approved dose of azithromycin for treatment of lower respiratory tract infections is 500 mg the first day followed by 250 mg for days 2 through 5. An alternative regimen for the treatment of AECB is 500 mg daily for 3 days. The recommended treatment of community-acquired pneumonia with the extended-release microsphere formulation of azithromycin is a single 2-g dose. The recommended dose of intravenous azithromycin for the treatment of community-acquired pneumonia is 500 mg daily for at least 2 days followed by oral azithromycin 500 mg daily to complete a 7- to 10-day course. Clarithromycin immediate- and extended-release tablets are approved for treatment of community-acquired pneumonia and AECB. The dose of the immediate-release tablets is 250 mg twice daily for 7 to 14 days. The dose should be increased to 500 mg if *H. influenzae* is being treated. The dose of the extended-release formulation is 2 × 500 mg tablets daily for 7 days. Telithromycin is FDA approved for the treatment of community-acquired pneumonia (including infections caused by multidrug-resistant *S. pneumoniae*) at a dose of 800 mg daily for 7 to 10 days.

**Sexually Transmitted Diseases**

The use of the advanced macrolides in the treatment of sexually transmitted diseases has focused primarily on azithromycin. The prolonged tissue half-life of azithromycin allows single-dose treatment courses, directly observed therapy, and improved patient compliance. A meta-analysis of randomized clinical trials concluded that a single 1-gram dose of azithromycin was equally efficacious and had similar tolerability as a standard 7-day regimen of doxycycline for the treatment of uncomplicated urethritis or cervicitis caused by *C. trachomatis*. Another meta-analysis for treatment
of *C trachomatis* infection during pregnancy found similar efficacy between a single 1-gram dose of azithromycin compared with erythromycin or amoxicillin. Guidelines published by the US Public Health Service (USPHS) currently recommend either doxycycline, 100 mg twice daily for 7 days, or azithromycin, 1 g as a single dose, for either chlamydial infections or nongonococcal urethritis among adolescents and adults. In a comparative study for the treatment of chronic prostatitis caused by *C trachomatis*, azithromycin (500 mg daily for 3 days on a weekly basis for 3 weeks) resulted in a significantly higher eradication rate and clinical cure compared with ciprofloxacin (500 mg twice daily for 20 days). Another trial showed equivalent outcomes between azithromycin (1 g weekly for 4 weeks) and doxycycline (100 mg twice daily for 28 days). A single 1-g dose of azithromycin is also one of the recommended treatments for genital ulcer disease caused by *H ducreyi* (chancroid).

Azithromycin has in vitro activity against *N gonorrhoeae*, and a single 2-g oral dose was found to be equally efficacious as ceftriaxone, 250 mg intramuscularly, in the treatment of uncomplicated gonorrhea. Gastrointestinal side effects occurred in 35% of patients who received azithromycin. The increased rate of side effects and greater expense of a 2-g azithromycin dose precluded the USPHS from recommending its use for the treatment of uncomplicated gonorrhea. If chlamydia infection is not ruled out in a patient with uncomplicated gonococcal urethritis or cervicitis, then either a single 1-g dose of azithromycin or 7-day course of doxycycline should be used in addition to the gonorrhea treatment regimen. Azithromycin with or without metronidazole has been shown to have similar clinical response rates to comparative agents (metronidazole + doxycycline + cefoxitin + probenicid or doxycycline + amoxicillin/clavulanate) in the treatment of pelvic inflammatory disease. The USPHS does not currently recommend this regimen for the treatment of pelvic inflammatory disease. Azithromycin resistance among gonococcal isolates is low in the United States, but 5.2% of isolates in Scotland had reduced susceptibility to azithromycin.

The use of azithromycin for the treatment of early syphilis also has been evaluated. A meta-analysis of four randomized controlled trials for the treatment of early syphilis concluded that azithromycin achieved a higher cure rate compared with penicillin G benzathine. A large comparative trial compared the efficacy of a single 2-g dose of azithromycin with an intramuscular injection of 2.4 million U of penicillin G benzathine. Cure rates at 3-, 6-, and 9-months were similar between the two treatment groups. Recently, a 23S rRNA gene mutation in *Treponema pallidum* conferring resistance to azithromycin was identified in 32 of 114 isolates (28%) obtained from four sexually transmitted disease clinics located in either the United States or Ireland. The USPHS does not currently recommend the use of azithromycin for the treatment of syphilis in the United States.

**Helicobacter Pylori Infections**

Antibiotic therapy for *H pylori*-associated peptic ulcer disease decreases ulcer recurrence and promotes healing. Triple-therapy regimens that consist of clarithromycin, amoxicillin, or metronidazole and an antisecretory agent for 7 to 14 days are preferable for the treatment of *H pylori* infections. These combinations maximize *H pylori* eradication, minimize the risk of antimicrobial resistance, and allow shorter and simplified treatment courses, which results in improved compliance. Clinical efficacy of different triple-therapy clarithromycin-based regimens for 7 to 14 days had cure rates of 70% to 80% based on intention-to-treat analyses. One meta-analysis and a recent randomized trial found that a 14-day course of clarithromycin triple therapy was more effective than a 7-day treatment course.
a proton pump inhibitor plus amoxicillin for 5 days followed by a proton pump inhibitor, clarithromycin, and tinidazole for 5 days for the treatment of *H pylori* was evaluated, mainly in Italy. Eradication rates of *H pylori* with the sequential regimen were 90% or more and were more effective than standard clarithromycin-based triple-therapy regimens. A recent meta-analysis concluded that sequential therapy seems to be superior to standard triple therapy, with crude eradication rates of *H pylori* of 93.4% and 76.9%, respectively.

Clarithromycin resistance rates vary in different regions of the world and, within a region, among different population subgroups. In the United States, the clarithromycin resistance rate among *H pylori* isolates was reported to be 13%. In a 15-year interval, the frequency of primary clarithromycin resistance in Italy increased from 10.2% (1989–1990) to 21.3% (2004–2005). *H pylori* resistance to clarithromycin has been shown to be associated with any previous use of macrolides. Pretreatment clarithromycin resistance has a negative impact on treatment efficacy (55% reduction in cure rates) and is associated with failure to eradicate *H pylori*.

In the United States, the American College of Gastroenterology practice guidelines recommend a clarithromycin-based regimen as one of two primary treatment options for *H pylori* infection. The recommended regimen includes a proton pump inhibitor, clarithromycin (500 mg twice daily), and either amoxicillin (1000 mg twice daily) or metronidazole (500 mg twice daily) given for 14 days. The alternative primary therapy recommended is a non–clarithromycin-based regimen that includes a proton pump inhibitor or ranitidine, bismuth subsalicylate, metronidazole, and tetracycline for 10 to 14 days. Until validation studies are conducted in other countries, the American College of Gastroenterology recommends that the sequential regimen outlined previously be considered as an alternative to the other standard first-line therapy options.

**MAC**

Clarithromycin and azithromycin have both been shown to be effective in preventing and treating disseminated MAC disease in HIV-infected patients. Azithromycin is effective as prophylaxis against disseminated MAC disease in patients with CD4 counts of less than 100 cells/mm³. In a comparative trial with rifabutin, the 1-year incidence rate of disseminated MAC disease was 15.3% in the rifabutin group (300 mg/d) compared with 7.6% in the azithromycin group (1200 mg weekly). Combination of azithromycin and rifabutin decreased the 1-year incidence rate of MAC to 2.8%, but 22.7% of patients discontinued therapy because of drug-related toxicity compared with 13.5% of patients who received azithromycin alone. Azithromycin resistance was seen in 11% of isolates obtained from patients who developed breakthrough disease. Similarly, clarithromycin was shown to be effective for MAC prophylaxis. In a comparative trial, clarithromycin (500 mg twice daily) was more effective in preventing MAC bacteremia than rifabutin (300 mg daily), with rates of 9% and 15%, respectively. Clarithromycin resistance was reported in 29% of the patients with breakthrough MAC bacteremia while on clarithromycin prophylaxis. Current USPHS/IDSA guidelines recommend either azithromycin, 1200 mg weekly, or clarithromycin, 500 mg twice daily, as the preferred regimens for MAC prophylaxis in HIV-infected individuals with a CD4 count of less than 50 cells/mm³.

The effectiveness of clarithromycin in combination with other antibiotics, especially ethambutol, for treatment of disseminated MAC disease in HIV-infected patients has been demonstrated in several randomized trials. A regimen of clarithromycin, rifabutin, and ethambutol was more effective in clearing MAC bacteremia and improving survival than a four-drug regimen of rifampin, ethambutol, clofazamine, and ciprofloxacin. Another trial compared dosing regimens of clarithromycin in combination with
ethambutol plus either rifabutin or clofazamine. Mortality was significantly higher at 4.5 months in patients who received clarithromycin at a dose of 1 g twice daily rather than the lower dose of 500 mg twice daily. In another trial that compared clarithromycin with rifabutin, ethambutol, or both, eradication of MAC bacteremia occurred in 40% to 50% of patients at 12 weeks of treatment. Response rates were not statistically different between the various treatment arms at 12 weeks. The relapse rate (24%) was higher in patients treated with clarithromycin and rifabutin than patients who received clarithromycin plus ethambutol (relapse rate 7%) or clarithromycin plus ethambutol plus rifabutin (relapse rate 6%).

Azithromycin, 600 mg daily, was compared with clarithromycin, 500 mg twice daily, for the treatment of disseminated MAC disease. Both were administered with ethambutol 15 mg/kg/d. Two consecutive sterile blood cultures at 24 weeks were obtained in 46% (31/68) of patients in the azithromycin group compared with 56% (32/57) in the clarithromycin group. There was no difference in mortality between the two treatment groups. Another study that used the same regimens found that clarithromycin was significantly better and more rapid in clearance of MAC bacteremia. Current recommendations for the treatment of disseminated MAC disease are to use at least two or more antimycobacterial drugs. Clarithromycin is the preferred first agent. Azithromycin is an alternative when drug interactions or intolerance preclude the use of clarithromycin.

Clarithromycin and azithromycin are also useful in the treatment of pulmonary MAC infections in HIV-negative patients. In noncomparative studies, sputum conversion rates at 6 months were comparable between azithromycin- and clarithromycin-containing regimens (67 versus 74%). The development of clarithromycin-resistant isolates was associated with microbiologic relapse. Intermittent treatment regimens also have been studied. Sixty-five percent of patients achieved treatment success with azithromycin-containing treatment regimens administered three times per week. Clarithromycin-containing regimens administered three times weekly resulted in a 78% sputum conversion to acid fast bacilli culture negative. Three times weekly clarithromycin therapy was less effective in patients with MAC infection and cavitory lung disease. The current ATS/IDSA guidelines recommend a three times weekly regimen, including clarithromycin, 1000 mg, or azithromycin, 500 mg, with ethambutol and rifampin for patients with nodular/bronchiectatic MAC lung disease. For patients with fibrocavitary or severe nodular/bronchiectatic MAC lung disease, the recommended regimen is daily dosing of clarithromycin, 500 to 1000 mg, or azithromycin, 250 mg, with ethambutol and rifampin.

**CLINICAL USE: TIGECYCLINE**

Tigecycline is FDA approved for the treatment of complicated skin and skin structure infections or complicated intra-abdominal infections. Two double-blind multicenter studies were conducted to evaluate the efficacy and safety of tigecycline monotherapy versus the combination of vancomycin and aztreonam for the treatment of hospitalized adults with complicated skin and skin structure infections. Tigecycline monotherapy was demonstrated to be noninferior to the combination of vancomycin and aztreonam; test-of-cure rates in the clinical evaluable population were 86.5% and 88.6%, respectively. Outcomes were similar between the two groups regardless of the type of skin and soft tissue infection present or bacterial species isolated. In another trial that compared tigecycline to vancomycin for the treatment of complicated skin and skin structure infections caused by methicillin-resistant *S aureus*, the clinical cure rates in the microbiologically evaluable population were 86.4% and 86.9% for tigecycline and vancomycin, respectively.
The efficacy of tigecycline was compared with imipenem/cilastatin in patients with complicated intra-abdominal infections in two double-blind randomized multicenter studies.\textsuperscript{183–185} In the microbiologically evaluable population, clinical cure rates were similar between tigecycline and imipenem/cilastatin (80.2% and 81.5%, respectively). Tigecycline cure rates were 80.6% versus 82.4% for imipenem/cilastatin, a statistically noninferior result. More than 80% of \textit{E. coli} and \textit{Klebsiella} spp (the most frequently isolated gram-negative aerobes) were eradicated by tigecycline; 78% of \textit{Streptococcus} spp and 70% of \textit{B. fragilis} were also eradicated.

Tigecycline has been evaluated against levofloxacin for the treatment of hospitalized patients with community-acquired pneumonia in two phase III, multicenter, double-blind studies. Pooled clinical cure rates were similar between the two treatment groups (89.7% and 86.3%). There were no significant differences in length of hospital stay, median duration of study antibiotic therapy, or hospital readmissions.\textsuperscript{186,187} Tigecycline received FDA approval for the treatment of community-acquired pneumonia in March, 2009.

Several studies evaluated the efficacy of tigecycline for the treatment of infections caused by MDR gram-negative organisms. Twenty-three of 33 patients treated with tigecycline had resolution of their infection caused by either a carbapenem-resistant or extended-spectrum beta lactamase-producing or MDR \textit{Enterobacteriaceae}.\textsuperscript{188} An open-label, Phase 3, noncomparative, multicenter study assessed the efficacy in hospitalized patients with serious infections primarily caused by complicated intra-abdominal infections, complicated skin and skin structure infections, or hospital-acquired pneumonia caused by resistant gram-negative organisms. In the microbiologically evaluable population, the clinical cure rate was 72.2% and the microbiologic eradication rate was 66.7%. The most commonly isolated resistant gram-negative pathogens were \textit{A. baumannii} (47%), \textit{E. coli} (25%), \textit{K. pneumoniae} (16.7%) and \textit{Enterobacter} spp (11%).\textsuperscript{189} In a retrospective study of 29 patients who received tigecycline for the treatment of acinetobacter infections, only 8 (28%) demonstrated clinical improvement or cure. None of the isolates was fully susceptible to tigecycline (median MIC 4 mg/L).\textsuperscript{190} In a small retrospective review of patients with serious infections caused by MDR gram-negative bacilli, pretherapy MIC values for tigecycline predicted clinical success.\textsuperscript{191,192}

**ADVERSE EFFECTS**

Gastrointestinal intolerance is the primary adverse side effect of the newer macrolides and ketolides, but they occur at a significantly reduced rate when compared with erythromycin. The most common adverse effects reported with azithromycin were diarrhea (3.6%), nausea (2.6%), abdominal pain (2.5%), and headache or dizziness (1.3%). Laboratory abnormalities were infrequent and minor, including transient increases in transaminases in 1.5% of patients. Only 0.7% of patients discontinued azithromycin therapy compared with 2.6% of patients who receive comparative medications.\textsuperscript{193} Gastrointestinal adverse effects (primarily diarrhea) occurred in 17% of patients treated with the 2-g extended-release microsphere formulation of azithromycin.\textsuperscript{83,102} Adverse events related to the intravenous infusion of azithromycin were pain at the injection site (6.5%) and local inflammation (3.1%).\textsuperscript{194} The most common adverse reactions reported with clarithromycin were similar (eg, nausea, 3.8%; diarrhea, 3.0%; abdominal pain, 1.9%; and headache, 1.7%).\textsuperscript{195} There was no difference in the spectrum and frequency of adverse reactions between the extended-release or immediate-release formulations of clarithromycin.\textsuperscript{20} Gastrointestinal adverse events with the extended-release formulation tended to be less severe and resulted in fewer discontinuations of the medication. Laboratory abnormalities were also rare and
included abnormal liver function test results and decreased white blood cell counts. Overall, less than 3% of patients receiving clarithromycin withdrew from studies because of adverse effects. Clarithromycin has been associated with teratogenic effects in animal studies and should not be used in pregnant patients.

In phase 3 clinical trials with telithromycin, the most common adverse effects reported were diarrhea (10.8%), nausea (7.9%), headache (5.5%), dizziness (3.7%), and vomiting (2.9%). These adverse effects were generally mild to moderate in severity and the number of patients discontinuing telithromycin (4.4%) was similar to those receiving comparator agents (4.3%). In a large study to assess clinical safety, more than 12,000 subjects with either community-acquired pneumonia or AECB received a course of telithromycin. Diarrhea occurred in 3.5% of study patients and gastrointestinal side effects occurred in 10.6%. Transient blurred vision occurred in 0.6% of telithromycin-treated patients. Clinical trials have shown a small increase (1.5 ms) in the QTc interval with telithromycin. No significant clinical effect on the QT interval in healthy adults was observed. Because of the potential risk of ventricular arrhythmias, however, telithromycin should be avoided in patients with congenital prolongation of the QT interval and patients with ongoing proarrhythmic conditions.

During clinical trials for treatment of community-acquired pneumonia, patients receiving telithromycin had a greater incidence of transient rises in hepatic transaminases compared with patients receiving alternative antibiotics. In the large clinical safety study mentioned previously, no clinically significant hepatic events were reported. An increase in alanine aminotransferase of more than 3 times upper limit of normal occurred in 1% of patients receiving telithromycin compared with 0.8% in patients receiving amoxicillin-clavulanic acid. Site investigations identified serious irregularities in the conduct of the trial, however, which raised concerns about the integrity of the study results.

Postmarketing surveillance reports described severe cases of hepatotoxicity in patients who received telithromycin. In a case series of 3 patients who developed acute hepatitis within days of receiving telithromycin therapy, one patient died and one required liver transplantation. Liver histology revealed inflammation consistent with a hypersensitivity reaction. By the end of 2006, telithromycin was implicated in 53 cases of hepatotoxicity, which included some fatalities. Telithromycin also was associated with myasthenia gravis exacerbations, including fatal and life-threatening acute respiratory failure. On February 12, 2007, the FDA removed telithromycin’s indication for the treatment of acute sinusitis and AECB and limited its approved indication to the treatment of community-acquired pneumonia alone. The FDA also issued a black box warning of the risk of respiratory failure in patients with myasthenia gravis and strengthened the warnings concerning the risk of acute hepatic failure and liver injury, which may be fatal.

The most common side effects associated with tigecycline use in clinical trials were nausea and vomiting, both of which were mild to moderate in intensity and transient. Overall, 29.5% of tigecycline recipients experienced nausea and 19.7% experienced vomiting. Diarrhea occurred in 13% of patients. Antimicrobial discontinuation as a result of an adverse event in these trials was similar between tigecycline recipients (5%) and the comparator antimicrobials (4.7%). There have been case reports of acute pancreatitis in patients treated with tigecycline. Because tigecycline is structurally similar to tetracyclines, it may have the same safety concerns. Tigecycline is labeled as a pregnancy category class D drug. Animal studies have shown that it crosses the placenta and is found in fetal tissues. Safety and efficacy of tigecycline in children younger than age 18 has not been established. As with tetracyclines, its use during tooth development may be associated with permanent tooth discoloration.
DRUG INTERACTIONS

Several reviews have discussed drug interactions between either clarithromycin or azithromycin and other agents.\textsuperscript{42,203} Clarithromycin, like erythromycin, is oxidized by the cytochrome P450 system, primarily the CYP3A4 subclass of hepatic enzymes. This converts clarithromycin to a nitrosalkalane metabolite that forms an inactive metabolite/enzyme complex by binding to the iron of the CYP3A4 enzyme. This interaction inhibits the CYP3A4 enzymes and results in decreased clearance of other agents given concurrently that are metabolized by the same enzyme system. Clarithromycin is a less potent inhibitor of the CYP 3A4 enzymes than erythromycin and azithromycin interferes poorly with this system.\textsuperscript{42}

Appropriate dose reductions and clinical and therapeutic drug level monitoring are necessary when drugs metabolized by the CYP3A enzymes are given concurrently with clarithromycin. The concurrent use of cisapride, pimozide, terfenadine, and azetemizole with clarithromycin is contraindicated because of the possible cardiotoxic effects of these agents and the occurrence of torsades de pointes. The concomitant administration of clarithromycin with ergotamine or dihydroergotamine is contraindicated because of the risk of acute ergot toxicity. Other medications such as benzodiazepines (eg, triazolam, midazolam, alprazolam), HMG-CoA reductase inhibitors (eg, lovastatin, simvastatin, atorvastatin), class 1A antiarrhythmic agents (eg, quinidine, disopyramide), theophylline, carbamazepine, warfarin, sildenafil, colchicine, and cyclosporine should be used cautiously when given with clarithromycin.\textsuperscript{19} These drug-drug interactions are less likely to occur with azithromycin, because it is not a potent inhibitor of the CYP3A enzymes. There are case reports of toxicity related to coadministration of azithromycin and lovastatin, warfarin, cyclosporine, disopyramide and theophylline, however.\textsuperscript{42,204} Clarithromycin and azithromycin have been associated with digoxin toxicity.\textsuperscript{205}

The potential for telithromycin to inhibit the cytochrome P450 3A4 pathway is comparable to clarithromycin, although metabolism of telithromycin does not result in the formation of nitrosalkalene metabolite. Telithromycin also competitively inhibits the CYP2D6 system. The concomitant administration of telithromycin with cisapride or pimozide is contraindicated. The use of HMG-CoA reductase inhibitors (simvastatin, lovastatin, or atorvastatin), rifampin, or ergot alkaloid derivatives with telithromycin should be avoided. Caution should be used when administering telithromycin with digoxin, midazolam, metoprolol, oral anticoagulants, or other drugs metabolized by the CYP3A4 enzymes.\textsuperscript{196}

Tigecycline does not interact with cytochrome P450 enzymes, making pharmacokinetic drug interactions uncommon. No significant drug interactions were noted during concomitant administration of tigecycline and digoxin or warfarin.\textsuperscript{206,207}

SUMMARY

The advanced macrolides (azithromycin and clarithromycin) and ketolides (telithromycin) are structural analogs of erythromycin that have similar mechanisms of action. These antimicrobials have several distinct advantages over erythromycin, including improved oral bioavailability, longer half-life (allowing once- or twice-daily administration), higher tissue concentrations, enhanced antimicrobial activity, and reduced gastrointestinal adverse effects. Clarithromycin and azithromycin have been used extensively for the treatment of upper and lower respiratory tract infections. Despite the increasing prevalence of macrolide resistance among \textit{S pneumoniae}, clinical failures have been reported infrequently. Treatment guidelines have solidified the roles of azithromycin in the treatment of certain sexually transmitted diseases and
clarithromycin for the treatment of *H pylori*-associated peptic ulcer disease. Azithromycin and clarithromycin have been used successfully to prevent and treat MAC infections.

Telithromycin has been shown to be clinically effective in the treatment of outpatient respiratory diseases. Because of safety concerns, however, especially the possibility of hepatotoxicity, the approved indication for telithromycin is limited to the treatment of community-acquired pneumonia. Tigecycline, a derivative of minocycline, has a broad spectrum of antimicrobial activity, including activity against many MDR pathogens. Tigecycline, available only as an intravenous preparation, is indicated for the treatment of complicated skin and skin structure and intra-abdominal infections. It is also approved for the treatment of community-acquired pneumonia. The role for tigecycline in the treatment of other types of infections with MDR organisms needs to be determined.

REFERENCES


47. Tygacil (tigecycline) prescribing information. 2008;2008(11/28).


96. Hoeffken G, Meyer HP, Winter J, et al. The efficacy and safety of two oral moxi-
floxacin regimens compared to oral clarithromycin in the treatment of commu-
study comparing clarithromycin extended-release tablets and levofloxacin
multicenter study comparing clarithromycin extended-release with trovafloxacin
dummy comparative study of gatifloxacin with clarithromycin in the treatment
100. Kinasewitz G, Wood RG. Azithromycin versus cefaclor in the treatment of acute
once daily for 3 days in the treatment of community-acquired pneumonia: an
open-label randomised comparison with amoxicillin-clavulanate 875/125 mg
102. Drehobl MA, De Salvo MC, Lewis DE, et al. Single-dose azithromycin micro-
spheres vs clarithromycin extended release for the treatment of mild-to-moderate
formulation of azithromycin versus 7-day levofloxacin therapy for treatment of
mild to moderate community-acquired pneumonia in adults. Antimicrob Agents
randomized controlled trials on the comparative efficacy and safety of azithro-
mycin against other antibiotics for lower respiratory tract infections. J Antimicrob
105. Panpanich R, Lertrakarnnon P, Laopaiboon M. Azithromycin for acute lower
for 3 days compared with clarithromycin for 10 days for acute exacerbation of
chronic bronchitis: a multicenter, double-blind, randomized study. Treat Respir
107. Amsden GW, Baird IM, Simon S, et al. Efficacy and safety of azithromycin vs lev-
ofloxacin in the outpatient treatment of acute bacterial exacerbations of chronic
108. Zervos M, Martinez FJ, Amsden GW, et al. Efficacy and safety of 3-day azithro-
mycin versus 5-day moxifloxacin for the treatment of acute bacterial exacerba-
625–33.
110. Pullman J, Champlin J, Vrooman PS Jr. Efficacy and tolerability of once-daily oral
therapy with telithromycin compared with trovafloxacin for the treatment of com-
111. Mathers Dunbar L, Hassman J, Tellier G. Efficacy and tolerability of once-daily oral
telithromycin compared with clarithromycin for the treatment of community-


123. Correa JC, Badaro R, Bumroongkit C, et al. Randomized, open-label, parallel-group, multicenter study of the efficacy and tolerability of IV gatifloxacin with the option for oral stepdown gatifloxacin versus IV ceftriaxone (with or without erythromycin or clarithromycin) with the option for oral stepdown clarithromycin for treatment of patients with mild to moderate community-acquired pneumonia requiring hospitalization. Clin Ther 2003;25(5):1453–68.


