

## Macrolides and ketolides: azithromycin, clarithromycin, telithromycin

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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 the penicillin-allergic patient. Additionally, erythromycin is effective for the treatment of infections caused by some intracellular pathogens, including species of *Legionella*, *Mycoplasma*, and *Chlamydia*. Several drawbacks, however, have limited the use of erythromycin, including frequent gastrointestinal intolerance and a short serum half-life.

Advanced macrolide antimicrobials have been synthesized by altering the erythromycin base resulting in compounds with extended spectrum of activity, favorable pharmacodynamics, once-a-day administration, and good tolerability. In 1991 and 1992, the US Food and Drug Administration (FDA) approved two of these agents, clarithromycin and azithromycin, 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* or *Mycobacterium avium* complex.

Ketolides, a new class of macrolides, share many of the characteristics of the advanced macrolides. Additionally, their *in vitro* spectrum of activity includes gram-positive organisms (*Streptococcus pneumoniae*, *Streptococcus pyogenes*), which are macrolide resistant. Telithromycin, specifically developed for the treatment of respiratory tract infections, has been approved for clinical use in Europe. It is under review by the FDA for final approval for clinical use in the United States. This article reviews the pharmacokinetics,

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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. The increased acid stability of clarithromycin 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 per 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 structural change makes the compound more stable in acid, significantly increases the serum half-life and tissue penetration, and results in increased activity against gram-negative organisms and decreased activity against some gram-positive organisms when compared with erythromycin [3]. Azithromycin is available as 250-, 500-, or 600-mg tablets; oral suspension (100–200 mg per 5 mL); and intravenous preparation (lyophilized 500 mg per 10 mL vial).

Ketolides, a new group of 14-membered macrolides, are synthesized by substituting a keto function for the  $\alpha$ -L-cladinose moiety at position 3 of the 14-membered erythronolide A ring [4]. This change promotes greater acid stability and prevents induction of macrolide-lincosamide-streptogramin B resistance [5]. Additionally, the hydroxyl group at position 6 of the erythronolide A ring is replaced by a methoxy group. Telithromycin is synthesized by cyclizing the C11-12 positions to form a carbamate ring with an imidazo-pyridyl group attachment. The 11,12 carbamate extension enhances binding to the bacterial ribosome and *in vitro* activity [6].

## **Mechanism of action and resistance**

The macrolide and ketolide antimicrobials exert their antibacterial effects by reversibly binding to the 50s subunit of the bacterial ribosome. This

interaction inhibits RNA-dependent protein synthesis by preventing transpeptidation and translocation reactions [2]. Both the macrolides and ketolides bind to domain V of the 23S ribosomal RNA (rRNA) [7]. The ketolides bind with a 10- to 100-fold higher affinity to the ribosome than erythromycin. Additionally, the ketolides, unlike the macrolides, have a greater affinity to bind to domain II of the 23S rRNA enabling it to maintain antimicrobial activity against bacterial strains that are macrolide resistant because of alterations in the domain V binding site [8].

Macrolide resistance in streptococci principally arises from either an alteration of the drug-binding site on the ribosome by methylation (macrolide-lincosamide-streptogramin B resistance) or by active drug efflux [9]. The efflux mechanism is mediated by the macrolide efflux (*mef*) genes and is specific for 14- and 15-membered macrolides [4]. 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 [10]. Resistance by methylation of an adenine residue in domain V of the 23S rRNA is mediated by the erythromycin ribosome methylase (*erm*) genes. Methylation prevents binding of the macrolides and ketolides to domain V and results in high-level macrolide resistance (MICs  $\geq$ 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 [11]. Methylase may either be induced or constitutively expressed, and resistance to erythromycin implies cross-resistance to clarithromycin and azithromycin [12]. Both clarithromycin and azithromycin can induce methylase production resulting in resistance. The 3-ketone substitution of telithromycin, however, does not induce methylase production [13]. Limited data are available regarding ketolide-specific mechanisms of resistance.

### Pharmacokinetics

The structural alterations to the erythromycin base used to synthesize the advanced macrolides and ketolides result in improved pharmacokinetic properties. Because erythromycin is degraded in an acidic environment, oral bioavailability is variable and depends on the preparation studied. Clarithromycin and azithromycin are more acid-stable and have greater oral bioavailability (55% and 37%, respectively) [14,15]. When taken with meals the peak plasma concentration of clarithromycin immediate-release tablets is increased by 24% but the overall bioavailability is unchanged [16]. Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract. The bioavailability of the extended-release formulation is equivalent to the immediate-release tablets when taken with food but is decreased by 30% when administered in the fasting state [17]. The extended-release formulations of clarithromycin should be administered with food, whereas the immediate-release tablets can be taken with or without food. The oral bioavailability of the

suspension formulation is similar to the equivalent tablet doses. The bioavailability of the tablet or suspension formulations of azithromycin is not affected by meals [18]. Aluminum- and magnesium-containing antacids reduce the peak serum concentrations of azithromycin but not the total absorption [19]. Oral absorption of an 800-mg dose of telithromycin is excellent (90%); however, 33% of the dose undergoes first-pass metabolism resulting in an absolute oral bioavailability of 57% [20]. The bioavailability, rate, and extent of absorption of telithromycin are unaffected by food [21].

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 of azithromycin following a 500-mg dose is approximately 0.4 mg/L, 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. An intravenous infusion of a 500-mg dose of azithromycin over 1 hour results in a peak serum concentration of 3.3 mg/L [22]. 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 [3]. Protein binding is higher for clarithromycin and telithromycin (60%–70%) compared with azithromycin (7%–50%).

Clarithromycin is metabolized to an active metabolite, 14-hydroxyclearithromycin. Larger doses of clarithromycin result in nonlinear increases in the serum half-life and in the area under the plasma concentration-time curve (AUC) of clarithromycin because of saturation of the metabolic pathway [23]. 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 [16]. Although steady-state peak plasma concentrations are lower and achieved later with the extended-

Table 1  
Comparative pharmacokinetics of macrolide antibiotics<sup>a</sup>

Parameter	Erythromycin		14-Hydroxy-		
	base	Azithromycin	Clarithromycin	clarithromycin	Telithromycin
Bioavailability	25	37	55	35	57
C <sub>max</sub> (mg/L)	0.3–0.9	0.4	2.1–2.4	0.6	1.9–2
t <sub>max</sub> (h)	3–4	2	2	2–3	1
t <sub>1/2</sub> (h)	2–3	40–68	3–5	4–7	7.16–13
AUC (mg/L x h)	8	3.4	19	5.7	7.9–8.25

*Abbreviations:* AUC, area under plasma concentration time curve; C<sub>max</sub>, peak serum concentration; t<sub>max</sub>, time to peak serum concentration; t<sub>1/2</sub>, serum half-life.

<sup>a</sup> Mean values after a single 500-mg oral dose (800-mg dose for telithromycin).

*Adapted from* Zhanell GG, Dueck M, Hoban DJ, et al: Review of macrolides and ketolides: focus on respiratory tract infections. *Drugs* 2001;61:443–98; with permission.

release formulation of clarithromycin than a comparable daily dose of the immediate-release formulations, the 24-hour AUC are equivalent between the two formulations supporting the once-daily dosing of the extended-release formulation [17]. With repeated dosing of intravenous azithromycin, the area under the curve (AUC) and serum half-life increased to 17.75 mg/Lxh and 76.8 hours, respectively [24]. Multiple doses of telithromycin, 800 mg daily, results in a steady-state peak plasma concentration of 2.27 mg/L and a terminal half-life of 9.81 hours [25].

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 [14,26]. Tissue concentrations do not peak until 48 hours after administration of azithromycin and persist for several days afterward [3]. Concentrations of clarithromycin and azithromycin in lung epithelial cell lining fluid exceed serum concentrations by 20-fold 24 hours after the last dose of drug administration [27]. Measurements at this interval reveal that alveolar macrophage concentrations are 400 times (clarithromycin) and 800 times (azithromycin) greater than their respective serum concentrations. Both drugs are also concentrated in polymorphonuclear cells [28].

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 (23 and 2.15 mg/L) 24 and 48 hours after dosing [29]. Concentrations of telithromycin in bronchial mucosa and epithelial lining fluid exceeded for 24 hours the mean MIC<sub>90</sub> of *S pneumoniae*, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae* [30]. In both these studies, concentrations of telithromycin in lung epithelial cell lining fluid exceeded serum concentrations by 12-fold 24 hours after the last dose of drug administration. Measurements at this interval revealed that alveolar macrophage concentrations are at least 400 times greater than their respective serum concentrations.

Clarithromycin is metabolized in the liver by the cytochrome P-450 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 [31]. The remainder is excreted into the bile. In patients with moderate-to-severe renal impairment (ie, creatinine clearance less than 30 mL/min), the dose should be reduced [31]. In patients with moderate-to-severe hepatic impairment and normal renal function, there is less metabolism of clarithromycin to the 14-hydroxy form resulting 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 [32].

Azithromycin elimination is primarily in the feces as the unchanged drug and urinary excretion is minimal [33]. Unlike clarithromycin, azithromycin

does not interact with the cytochrome P-450 system [34]. In patients with mild or moderate hepatic impairment, dosing modifications do not seem to be necessary [35].

Telithromycin is eliminated by multiple pathways including unchanged drug in feces (7%) and urine (13%) and the remainder by hepatic metabolism by the CYP3A4 and 1A isoenzymes [36]. Approximately 17% of a single 800-mg dose is excreted in the urine and the rest in the feces. There are four metabolites of telithromycin that do not have appreciable antibacterial activity [11]. 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 [11]. Dosing modifications are not necessary when administering telithromycin to patients with hepatic impairment because pharmacokinetics are not significantly changed due to a compensatory increase in renal excretion [37].

### Spectrum of activity

Guidelines from the National Committee for Clinical Laboratory Standards provide the following interpretation of in vitro MICs for clarithromycin and azithromycin [38]. For *S pneumoniae*, susceptibility breakpoints are less than or equal to 0.25 mg/L and less than or equal to 0.5 mg/L for clarithromycin and azithromycin, respectively. The corresponding resistance breakpoints are greater than or equal to 1 mg/L and greater than or equal to 2 mg/L. The breakpoint for susceptibility against *Staphylococcus aureus* occurs at a MIC of less than or equal to 2 mg/L and resistance at a MIC greater than or equal to 8 mg/L. *Haemophilus* spp are considered susceptible to clarithromycin at a MIC less than or equal to 8 mg/L and resistant at a MIC greater than or equal to 32 mg/L and susceptible to azithromycin at a MIC less than or equal to 4 mg/L. Proposed breakpoints for telithromycin against streptococci and staphylococci are susceptibility at less than or equal to 1 mg/L and resistance at greater than or equal to 4 mg/L. *Haemophilus influenzae* is considered susceptible to telithromycin at less than or equal to 2 mg/L and resistant at greater than or equal to 8 mg/L [39,40].

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, however, account for the antimicrobial activity of the active 14-hydroxy metabolite and may underestimate the activity of clarithromycin [41]. Results of MIC testing vary with testing conditions. An increased pH or addition of serum can decrease the MIC measured, whereas incubation in a CO<sub>2</sub> environment increases the MIC measured [42]. Comparative in vitro susceptibility data for erythromycin, clarithromycin, azithromycin, and telithromycin are shown in Table 2.

Table 2  
Comparative in vitro activities of macrolide-ketolide antibiotics<sup>a</sup>

Organism	Erythromycin	Azithromycin	Clarithromycin	Telithromycin
Gram-positive aerobes				
<i>Streptococcus pyogenes</i>				
(erythromycin susceptible)	0.06–0.12	0.12–0.25	0.06–0.12	0.03
( <i>ermA</i> resistance)	1–32	16–32	2–16	0.015–0.25
( <i>ermB</i> resistance)	>64	>64	>64	>8
( <i>mefA</i> resistance)	8–16	8	8–16	0.25–1
<i>Streptococcus pneumoniae</i>				
(erythromycin sensitive)	0.03–0.12	0.06–0.25	0.03–0.12	0.008–0.03
(erythromycin resistant <i>ermB</i> )	≥32	≥64	≥64	0.125–0.5
(erythromycin resistant <i>mefA</i> )	8–16	8–16	8	0.25–1
Gram-negative aerobes				
<i>Haemophilus influenzae</i>	8	2–4	4–16	2–4
<i>Moraxella catarrhalis</i>	0.125–0.25	0.06–0.12	0.12–0.25	0.12
<i>Legionella pneumophila</i>	0.12–2	0.25–2	0.06–0.25	0.015–0.06
<i>Neisseria gonorrhoeae</i>	0.5	0.25		0.12
Other pathogens				
<i>Chlamydomphila pneumoniae</i>	0.06–0.25	0.125–0.25	0.03–0.06	0.06–0.25
<i>Mycoplasma pneumoniae</i>	≤0.015–0.06	≤0.015	≤0.015–0.03	≤0.015

<sup>a</sup> Values expressed as MIC<sub>90</sub> (mg/L); ranges are caused by the different values reported in references.

Data from Refs. [4,36,39,167–170].

Clarithromycin demonstrates equal or better in vitro activity against gram-positive organisms compared with erythromycin. Azithromycin, by comparison, is twofold to fourfold less active than erythromycin against these gram-positive organisms but the MICs are still within achievable therapeutic levels [43]. Azithromycin and clarithromycin are generally inactive against methicillin-resistant staphylococci. Staphylococci and streptococci that are resistant to erythromycin are also resistant to azithromycin and clarithromycin [41].

Telithromycin is more active in vitro against *S pneumoniae* compared with clarithromycin and azithromycin and maintains activity against strains that are macrolide resistant [44]. In one in vitro study, the MIC<sub>90</sub> for telithromycin against *S pneumoniae* strains with the *mefA* gene was less than or equal to 0.25 mg/L compared with 1 to 4 mg/L for macrolides. Against strains expressing the *ermB* gene, telithromycin had an MIC<sub>90</sub> of 0.5 mg/L, whereas the macrolides had an MIC<sub>90</sub> greater than 64 mg/L [45]. Telithromycin MIC<sub>90</sub> increased from 0.015 to 0.25 and 0.5 mg/L for penicillin-intermediate and penicillin-resistant pneumococcal strains, respectively [46]. It is unclear whether the continued in vitro activity of telithromycin against macrolide-resistant *S pneumoniae* provides a clinical advantage for the treatment of infections caused by these resistant isolates. Telithromycin is also twofold 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 MLS<sub>B</sub> gene but not against strains where resistance is constitutively expressed [9].

The newer macrolides demonstrate enhanced activity against *H influenzae*. Clarithromycin has similar activity as erythromycin against *H influenzae*. When combined with its active metabolite 14-hydroxyclearithromycin, however, synergistic or additive activity occurs and the MIC decreases twofold to fourfold [47]. Azithromycin and telithromycin are more active against *H influenzae* with a MIC fourfold to eightfold lower compared with erythromycin [48]. The advanced macrolides and ketolides also demonstrate enhanced activity against other respiratory pathogens. Clarithromycin seems more active than azithromycin and erythromycin against *Legionella pneumophila* and *Chlamydia pneumoniae*, whereas azithromycin demonstrates better in vitro activity against *M catarrhalis* and *M pneumoniae* [43,49]. Telithromycin has excellent in vitro activity against *Mycoplasma*, *Chlamydia*, and *Legionella* and is more active compared with the macrolides [36].

Azithromycin has activity against enteric pathogens including *Escherichia coli*, *Salmonella* spp, *Yersinia enterocolitica*, and *Shigella* spp [43]. 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 *Helicobacter pylori* [50,51].

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 better activity as evidenced by a lower MIC [50,51]. Clarithromycin is approximately 10-fold more active than erythromycin against *Chlamydia trachomatis*; whereas azithromycin activity is similar to that of erythromycin [50,51]. Only azithromycin demonstrated in vitro activity against *Mycoplasma hominis* [41].

As discussed previously, the advanced macrolides and ketolides achieve concentrations in tissues and phagocytes that far exceed serum concentrations. In vitro MIC measurements 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. An in vitro study demonstrated the effects of clarithromycin or azithromycin at concentrations achieved in the lung epithelial lining fluid against *H influenzae* and *S pneumoniae* [52]. At these concentrations, clarithromycin demonstrated a significantly longer postantibiotic effect against *S pneumoniae* compared with azithromycin. Azithromycin demonstrated more rapid killing and longer postantibiotic effect against *H influenzae* compared with clarithromycin. Telithromycin also demonstrates a postantibiotic effect that seems to be concentration dependent [53].

## Clinical use

### *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 either 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 [3,54–56]. In comparative trials, clarithromycin has proved to be equivalent to amoxicillin, amoxicillin-clavulanate, and cefaclor for the treatment of acute otitis media in children [50,57]. Otitis media in children was also treated equally as well with azithromycin (3 or 5 days) or 10 days of either amoxicillin-clavulanate or cefaclor [58]. A recent trial found that a single oral dose of azithromycin at 30 mg/kg was effective for the treatment of otitis media [59].

Clarithromycin has been shown to have equivalent efficacy for the treatment of acute sinusitis compared with cefuroxime axetil, levofloxacin, sparfloxacin, or ciprofloxacin [60–63]. A 14-day course of either the immediate-release or extended-release formulations of clarithromycin was comparable in the treatment of acute maxillary sinusitis in adults [64]. A 3-day regimen of azithromycin (500 mg daily) was equally as efficacious as a 10-day course of amoxicillin-clavulanate in acute sinusitis [65–67]. In a noncomparative trial, both a 5- and 10-day course of telithromycin was comparable with clinical and bacteriologic eradication rates of 91% [68]. A 5-day course of telithromycin was equally as effective as 10-day course of amoxicillin-clavulanate or cefuroxime axetil [69].

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 or 2 × 500 mg every 24 hours with the extended-release tablets for 14 days. For children, the recommended dose is 7.5 mg/kg every 12 hours. Azithromycin is approved for the treatment of pharyngitis and otitis media. 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 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. For the treatment of pharyngitis, 12 mg/kg per day should be given for 5 days. FDA approval is being sought for use of telithromycin for the treatment of acute sinusitis.

#### *Lower respiratory tract infections*

Various trials have demonstrated the efficacy of clarithromycin and azithromycin for treatment of lower respiratory tract infections including

acute bronchitis, acute exacerbation of chronic bronchitis (AECB), and community-acquired pneumonia (CAP). Most of the 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 [70]. 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 [71–75]. Clinical cure rates for the treatment of AECB were similar between a 10-day course of clarithromycin, levofloxacin, or cefuroxime axetil, and also between a 7-day course of extended-release tablets of clarithromycin or amoxicillin-clavulanic acid [73,76,77]. In a comparative trial between 5 days of gemifloxacin and 7 days of clarithromycin for the treatment of AECB, clinical and bacteriologic cures were similar but significantly more patients in the gemifloxacin group remained free of AECB recurrences [78]. Comparative trials for the outpatient treatment of CAP have shown equivalent efficacy between clarithromycin, 500 mg twice a day for 10 days and moxifloxacin, and clarithromycin extended-release tablets (2 × 500 mg tablets once daily for 7 days) and levofloxacin or trovafloxacin [79–81]. In a noncomparative trial, clarithromycin (500 to 1000 mg twice a day for 14 to 35 days) was effective in 43 of 44 patients with *Legionella* pneumonia [82].

Azithromycin (500 mg on day 1 followed by 250 mg daily for 4 days) has been found to be equivalent to cefaclor in patients with outpatient CAP [83]. The use of a 3-day course of azithromycin (500 mg daily) for the treatment of lower respiratory tract infections seems to have equivalent efficacy compared with longer courses of other antimicrobial agents [84]. In two comparative studies, azithromycin (500 mg daily for 3 days) was as efficacious as clarithromycin (250 mg twice a day for 10 days) in the treatment of patients with lower respiratory tract infections [85,86]. A meta-analysis of randomized controlled trials of azithromycin compared with other antibiotics showed comparable clinical cures in the treatment of acute bronchitis and AECB and superior efficacy in the treatment of CAP [87]. A recent trial demonstrated equivalent efficacy between 5-day course of azithromycin and a 7-day course of levofloxacin for the treatment of AECB [88].

Telithromycin has demonstrated excellent clinical efficacy in the outpatient treatment of CAP in both open-label studies and comparator trials. Telithromycin was equally as effective when compared with either a 10-day course of high-dose amoxicillin, twice-daily clarithromycin, or a 7- to 10-day course of trovafloxacin (clinical cure rates 88%–95%) [89–92]. Clinical cure rates and bacterial eradication were comparable in patients treated with either a 7- or 10-day course of telithromycin [93]. Forty-four of 55 patients with erythromycin-resistant *S pneumoniae* infections were cured including 8 of 10 patients with bacteremia [11,94]. For the treatment of AECB, a 5-day

course of telithromycin was found to be equally as effective as a 10-day course with either cefuroxime axetil, clarithromycin, or amoxicillin-clavulanate [95]. In several studies, however, eradication rates for *H influenzae* were lower for telithromycin (66%) than comparators (88%) [40].

Azithromycin and clarithromycin have also been shown to be effective in the treatment of CAP in patients requiring hospitalization. Monotherapy with intravenous azithromycin was equally as effective as cefuroxime plus or minus erythromycin followed by their oral equivalents to complete a 7- to 10-day course of therapy [96,97]. Comparing these regimens, azithromycin monotherapy was associated with lower costs, decreased duration of therapy, and reduced hospital length of stay [98]. In a retrospective review of patients hospitalized with CAP, outcomes were similar between patients who received azithromycin monotherapy compared with treatment with a respiratory fluoroquinolone or a  $\beta$ -lactam plus macrolide regimen [99]. Recent comparative trials have shown equivalent efficacy between respiratory fluoroquinolones and ceftriaxone plus azithromycin or clarithromycin in patients with CAP requiring hospitalization [100,101]. Other studies imply an advantage in dual empiric therapy, which includes a macrolide, in reducing mortality in patients with bacteremic pneumococcal pneumonia [102,103]. A retrospective analysis of empiric treatments for pneumonia in hospitalized Medicare patients ( $\geq 65$  years of age) revealed that 30-day mortality rates were significantly lower for those patients whose initial empiric treatment regimens were either a macrolide plus a second- or third-generation cephalosporin or a respiratory fluoroquinolone alone [104]. Treatment with azithromycin alone was used in a limited number of patients in this population and could not be adequately assessed. Azithromycin monotherapy successfully treated 96% (22 of 23) of patients hospitalized with *L pneumonia* with a mean total duration of antibiotic therapy (intravenous plus oral) of 7.92 days [105]. There are limited published data on the use of telithromycin for treatment of CAP in hospitalized patients.

Pneumococcal resistance to macrolides is becoming more prevalent. In the United States, 26% of *S pneumoniae* isolates from 1999 to 2000 were macrolide resistant, an increase from 10.3% of isolates during the period of 1994 to 1995 [46]. Rates of macrolide resistance were higher for nonsusceptible penicillin isolates compared with susceptible ones and all isolates were sensitive in vitro to telithromycin [46]. In 2001, rates of erythromycin resistance in Canada and the United States were 16.3% and 31.5%, respectively [106]. In the United States, two thirds of the macrolide-resistant isolates exhibit low-level erythromycin resistance by expression of the *mef(A)* gene, whereas the remainder expresses the *erm(B)* gene resulting in high-level resistance [46,107]. The prevalence of erythromycin resistance among *S pneumoniae* isolates varies greatly among geographic regions [108]. The region with the highest prevalence of resistance reported is Taiwan where 92% of clinical *S pneumoniae* isolates exhibited erythromycin resistance and 16% of the isolates exhibited telithromycin resistance (MIC

$\geq 1$  mg/L) [109]. All of the telithromycin-resistant isolates were of the constitutive macrolide-lincosamide-streptogramin B phenotype.

Despite the high prevalence of macrolide resistance, reported clinical failures have been limited to small case series. Breakthrough bacteremia with macrolide-resistant *S pneumoniae* strains has been reported in patients who failed outpatient therapy with either clarithromycin or azithromycin [110,111]. 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 [112]. 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  $\beta$ -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 provide recommendations for the empiric treatment of CAP based on the clinical setting [113,114]. Preferred regimens are stratified according to the setting of antimicrobial therapy (ambulatory versus hospitalized); the likelihood of an atypical pathogen (*Legionella*, *Chlamydia*, *Mycoplasma*); and the presence of risk factors for drug-resistant *S pneumoniae*. These risk factors vary between the guidelines. Risk factors for drug-resistant *S pneumoniae* in the American Thoracic Society guidelines include the presence of comorbidities (diabetes, chronic obstructive pulmonary disease, congestive heart failure, and so forth); age greater than 65; alcoholism; immunosuppression; or recent (within the past 3 months) antibiotic use. The IDSA guidelines consider recent antibiotic use as the primary risk factor for drug-resistant *S pneumoniae*. Only those treatment options that include a macrolide are discussed and the reader is referred to the guidelines for alternative options.

Outpatient therapy in the IDSA guidelines for patients who have not received antibiotics within the previous 3 months includes any macrolide (erythromycin, azithromycin, or clarithromycin) for previously healthy individuals, or an advanced macrolide (azithromycin or clarithromycin) if they have comorbid conditions. If there was recent antibiotic use, however, then an advanced macrolide should be used in combination with a  $\beta$ -lactam. The American Thoracic Society guidelines recommend macrolide plus  $\beta$ -lactam outpatient therapy for all patients except for those without cardiopulmonary disease or other modifying risk factors for drug-resistant *S pneumoniae*. For patients who require hospitalization, an advanced macrolide combined with a  $\beta$ -lactam is one of the preferred regimens

recommended by both guidelines. Azithromycin monotherapy is not recommended by the IDSA for hospitalized patients but is an option recommended by the American Thoracic Society for those patients without any risk factors for drug-resistant *S pneumoniae*.

The FDA-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 dose of intravenous azithromycin for the treatment of CAP 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 CAP and acute exacerbation of chronic bronchitis. 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  $2 \times 500$  mg tablets daily for 7 days. Final FDA approval is being sought for use of telithromycin for the treatment of AECB and CAP.

### *Sexually transmitted diseases*

The use of the advanced macrolides in the treatment of sexually transmitted diseases has focused primarily on azithromycin. The unique pharmacokinetics of azithromycin, including high tissue concentrations and a prolonged tissue half-life, allows single-dose treatment courses, directly observed therapy, and improved patient compliance. A meta-analysis of randomized clinical trials concluded that a single 1-g 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* [115]. Guidelines published by the US Public Health Service currently recommend either doxycycline, 100 mg twice a day for 7 days, or azithromycin, 1 g as a single dose, for either chlamydial infections or nongonococcal urethritis among adolescents and adults [116]. Data suggest that azithromycin may be an effective and safe alternative for the treatment of cervical chlamydial infection during pregnancy [117,118]. 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) [119]. A single 1-g dose of azithromycin is also one of the recommended treatments for genital ulcer disease caused by *H ducreyi* (chancroid) [116].

Azithromycin has in vitro activity against *N gonorrhoeae* and successfully eradicated the organism in 85 (93%) of 91 patients with positive urethral or cervical cultures [120]. Azithromycin, 2 g orally, was found to be equally as efficacious as ceftriaxone, 250 mg intramuscularly, in the treatment of uncomplicated gonorrhea [121]. Gastrointestinal side effects, however,

occurred in 35% of patients receiving azithromycin. The increased rate of side effects and greater expense of a 2-g azithromycin dose precluded the US Public Health Service from currently recommending the use of azithromycin for the treatment of uncomplicated gonorrhea [116]. 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 treatment regimen for the gonorrhea infection. Azithromycin with or without metronidazole has been shown to have similar clinical response rates to comparative agents (metronidazole plus doxycycline plus cefoxitin plus probenecid or doxycycline plus amoxicillin-clavulanate) in the treatment of pelvic inflammatory disease [122]. Azithromycin was administered as 500 mg intravenously daily for 1 to 2 days followed by a daily oral dose of 250 mg to complete a 7-day course. The US Public Health Service does not currently recommend this regimen for the treatment of pelvic inflammatory disease.

A few studies have evaluated the use of azithromycin for the treatment of early syphilis. An open, noncomparative study of azithromycin, 1 g on day 1 followed by 500 mg for 8 days, successfully treated patients with either primary or secondary syphilis [123]. A small comparative trial compared intramuscular injections of 2.4 million units of benzathine penicillin G, a single 2-g dose of azithromycin, and two 2-g doses of azithromycin given 1 week apart. Treatment responders, defined as patients whose rapid plasma reagin test became nonreactive or titer decreased by greater than or equal to two dilutions within 12 months, occurred in 86% (12 of 14) of the penicillin group; 94% (16 of 17) in the single-dose azithromycin group; and 83% (24 of 29) in the two-dose azithromycin group [124]. A single 2-g dose may be a possible alternative regimen for the treatment of early syphilis in patients who are allergic to penicillin [116]; however, recent failures have been reported [125]. A single 1-g dose of azithromycin was efficacious in preventing syphilis in 40 patients exposed to infected sexual partners [126].

### *Skin and soft tissue infections*

Azithromycin and clarithromycin have been approved for use in skin and soft tissue infections. Azithromycin (1.5 g administered over 3 or 5 days) was equivalent to a 7-day course of dicloxacillin or a 10-day course of cephalexin in the treatment of adult skin and soft tissue infection [127,128]. Similarly in children, azithromycin was equally as effective as either dicloxacillin or cefaclor [129,130]. Clarithromycin was equivalent to erythromycin or cefadroxil in the treatment of skin infections [131].

### *Helicobacter pylori infections*

Numerous studies have documented the efficacy of clarithromycin in the treatment of *H pylori* infections associated with peptic ulcer disease.

Antibiotic therapy for *H pylori*-associated peptic ulcer disease decreases ulcer recurrence and promotes healing. Several dual treatment regimens (clarithromycin, 500 mg three times a day, in combination with either ranitidine bismuth citrate or omeprazole) have received FDA approval [132]. However, many authors recommend triple therapy regimens consisting of at least two antibiotics with one antisecretory agent for 7 to 14 days [132–134]. These combinations maximize *H pylori* eradication, minimize the risk of antimicrobial resistance, and allow shorter and simplified treatment courses resulting in improved compliance. A large meta-analysis study showed that the efficacy of different triple-therapy regimens (proton-pump inhibitor plus clarithromycin plus amoxicillin, proton-pump inhibitor plus clarithromycin plus nitroimidazole, or proton-pump inhibitor plus amoxicillin plus nitroimidazole) had similar rates of cure of 78.9% to 82.8% based on intent-to-treat analyses [135]. Efficacy is similar among different proton-pump inhibitors when used with clarithromycin plus either amoxicillin or metronidazole [136]. Triple-drug therapies approved by the FDA include a twice-daily regimen of a proton pump inhibitor (lansoprazole [30 mg] or omeprazole [20 mg] or esomeprazole [40 mg daily]) plus clarithromycin (500 mg) and amoxicillin (1 g) for 10 days [132].

Clarithromycin-based treatment regimens of 7 days duration have also been extensively studied and shown to have a mean *H pylori* eradication rate of 81% on intent-to-treat basis [137]. Clarithromycin at a dose of 500 mg achieved slightly higher eradication rates when compared with similar regimens using 250 mg clarithromycin [138]. Triple-based clarithromycin regimens were comparable when either ranitidine bismuth citrate or an H<sub>2</sub>-receptor antagonist was substituted for a proton-pump inhibitor [139, 140]. A pooled analysis showed no significant difference in efficacy between 1-week courses of either a triple-therapy regimen (clarithromycin, amoxicillin, and a proton-pump inhibitor) or a quadruple-therapy regimen (proton-pump inhibitor, tetracycline, metronidazole, and a bismuth salt) [141].

The optimal duration of therapy for *H pylori* infections has yet to be determined; 7-day treatment regimens are generally recommended in Europe, whereas 14-day regimens are used in the United States [134,142]. One meta-analysis suggested that cure rates were 7% to 9% better in regimens lasting 14 days compared with ones of 7 days duration [143]. Shorter treatment regimens tend not to be as efficacious in areas with increased prevalence of clarithromycin resistance. A pooled analysis of 20 clinical trials of *H pylori* eradication in the United States from 1993 to 1999 revealed that 10.1% of pretreatment isolates were resistant to clarithromycin (MIC  $\geq$  1 mg/L) [144]. Clarithromycin resistance was significantly more likely in the mid-Atlantic and northeastern regions of the United States, older patients, women, and patients with an inactive ulcer. *H pylori* resistance to clarithromycin has also been shown to be associated with any previous use of macrolides [145]. Pretreatment clarithromycin resistance

is associated with a negative impact on treatment efficacy (55% reduction in cure rates) and failure to eradicate *H Pylori* [146].

In the United States, practice guidelines from the American College of Gastroenterology recommend the following clarithromycin-containing regimens: a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole; or ranitidine bismuth citrate, clarithromycin, and either amoxicillin, metronidazole, or tetracycline [134]. Treatment courses are for 14 days and all agents are given twice daily.

### *Mycobacterium avium complex and HIV infection*

Clarithromycin and azithromycin have been shown to be effective in preventing and treating disseminated *M avium* complex disease in HIV-infected patients. Azithromycin is effective as prophylaxis against disseminated *M avium* complex disease in patients with CD4 counts less than 100 cells/mm<sup>3</sup>. Compared with placebo, a 1200-mg weekly dose decreased the incidence of disseminated *M avium* complex from 24.7% to 10.6% [147]. In a comparative trial with rifabutin, the 1-year incidence rate of disseminated *M avium* complex 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 of *M avium* complex to 2.8% but 22.7% of patients discontinued therapy because of drug-related toxicity compared with 13.5% of patients receiving azithromycin alone. Azithromycin resistance was seen in 11% of isolates obtained who developed breakthrough disease. Similarly, clarithromycin, 500 mg twice a day, compared with placebo was effective in preventing *M avium* complex bacteremia, 6% and 16%, respectively, and decreasing overall mortality, 31% versus 42% [149]. Eleven of the 19 patients with breakthrough *M avium* complex bacteremia had isolates that were resistant to clarithromycin. In a comparative trial, clarithromycin (500 mg twice daily) was more effective in preventing *M avium* complex bacteremia than rifabutin (300 mg daily), 9% and 15%, respectively [150]. Clarithromycin resistance was reported in 29% of the patients with breakthrough *M avium* complex bacteremia while on clarithromycin prophylaxis. Current US Public Health Service–IDSA guidelines recommend azithromycin, 1200 mg weekly, or clarithromycin, 500 mg twice a day, as the preferred regimens for *M avium* complex prophylaxis in HIV-infected individuals with a CD4 count less than 50 cells/mm<sup>3</sup> [151].

The effectiveness of clarithromycin in combination with other antibiotics, especially ethambutol, for treatment of disseminated *M avium* complex disease in HIV-infected patients has been demonstrated in several randomized trials [152–154]. A regimen of clarithromycin, rifabutin, and ethambutol was more effective in clearing *M avium* complex bacteremia and improving survival than a four-drug regimen of rifampin, ethambutol, clofazimine, and ciprofloxacin [155]. Another trial compared dosing

regimens of clarithromycin in combination with ethambutol plus either rifabutin or clofazimine. Mortality was significantly higher at 4.5 months in those patients who received clarithromycin at a dose of 1 g twice a day rather than the lower dose of 500 mg twice a day [156]. In another trial comparing clarithromycin with rifabutin, ethambutol, or both, eradication of *M avium* complex bacteremia occurred in 40% to 50% of patients at 12 weeks of treatment [157]. Response rates were not statistically different between the various treatment arms at 12 weeks. The relapse rate (24%), however, was higher in patients treated with clarithromycin and rifabutin than patients receiving clarithromycin plus ethambutol (relapse rate 7%) or clarithromycin plus ethambutol plus rifabutin (relapse rate 6%). In one study azithromycin, 600 mg daily, was compared with clarithromycin, 500 mg twice a day [158]. Both were administered with ethambutol, 15 mg/kg/d. Two consecutive sterile blood cultures at 24 weeks were obtained in 46% (31 of 68) of patients in the azithromycin group compared with 56% (32 of 57) in the clarithromycin group. There was no difference in mortality between the two treatment groups. Another study using the same regimens, however, found that clarithromycin was significantly better and more rapid in clearance of *M avium* complex bacteremia [159].

### Adverse effects

Azithromycin, clarithromycin, and telithromycin are well tolerated. Gastrointestinal intolerance is the primary adverse side effect of these agents, but occurs at a significantly reduced rate when compared with erythromycin [41]. 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 receiving comparative medications [19]. Adverse events related to the intravenous infusion of azithromycin were pain at the injection site (6.5%) and local inflammation (3.1%) [22]. The most common adverse reactions reported with clarithromycin were similar (eg, nausea [3.8%], diarrhea [3%], abdominal pain [1.9%], and headache [1.7%]) [160]. There was no difference in the spectrum and frequency of adverse reactions between the extended-release or immediate-release formulations of clarithromycin [17]. Gastrointestinal adverse events with the extended-release formulation, however, tended to be less severe and resulted in fewer discontinuations of the medication. Laboratory abnormalities were also rare and included abnormal liver function tests and decreased white blood cell counts. Overall, fewer than 3% of patients receiving clarithromycin withdrew from studies because of adverse effects [42].

In phase 3 clinical trials (N = 2702) 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%) [11]. 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, 12,159 subjects with either CAP or AECB received a course of telithromycin. Diarrhea occurred in 3.5% of study patients and gastrointestinal side effects in 10.6%. Transient blurred vision occurred in 0.6% of telithromycin-treated patients [11].

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 [161]. During clinical trials for treatment of CAP, patients receiving telithromycin had a greater incidence of transient rises in hepatic transaminases compared with patients receiving alternative antibiotics [4]. In a large clinical safety study and postmarketing surveillance, no clinically significant hepatic events were reported. An increase in alanine transaminase greater than three times upper limit of normal (ULN) occurred in 1% of patients receiving telithromycin compared with 0.8% in patients receiving amoxicillin-clavulanic acid [11].

### **Drug interactions**

Several reviews have discussed drug interactions between either clarithromycin or azithromycin and other agents [34,162]. Clarithromycin, like erythromycin, is oxidized by the cytochrome P-450 system, primarily the CYP3A4 subclass of hepatic enzymes [163]. This converts clarithromycin to a nitrosalkalane metabolite that forms an inactive metabolite-enzyme complex by binding to the iron of the CYP3A4 enzyme [34]. This interaction inhibits the CYP3A4 enzymes resulting in decreased clearance of other agents given concurrently that are metabolized by the same enzyme system. Clarithromycin is a less potent inhibitor of the CYP3A4 enzymes than erythromycin and azithromycin interferes poorly with this system [34].

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, pimozone, terfenadine, and astemizole with clarithromycin is contraindicated because of the possible cardiotoxic effects of these agents and the occurrence of torsades de pointes [16]. Other medications, such as benzodiazepines (triazolam, midazolam, and alprazolam), 3-hydroxy-3methylglutaryl-coenzyme A reductase inhibitors (lovastatin, simvastatin, and atorvastatin), class 1A antiarrhythmic agents (quinidine, disopyramide), theophylline, carbamazepine, warfarin, ergots, and cyclosporine should be used cautiously when given with clarithromycin. These drug-drug interactions are less likely to occur with azithromycin because it is not a potent inhibitor of the CYP3A enzymes [15,164]. There are case reports, however, of toxicity related to coadministration of azithromycin and lovastatin,

warfarin, cyclosporine, disopyramide, and theophylline [34]. Both clarithromycin and azithromycin have been associated with digoxin toxicity [165]. In a study of healthy volunteers, coadministration of clarithromycin with oral digoxin resulted in a 1.7-fold increase in the AUC<sub>24</sub> of digoxin and a reduction of the nonglomerular renal clearance of digoxin, but after intravenous administration of digoxin, the digoxin AUC<sub>24</sub> increased only 1.2-fold [166]. The authors postulated that clarithromycin inhibits intestinal and renal P-glycoprotein (an ATP-dependent efflux drug transporter) resulting in increased oral bioavailability and reduced nonglomerular renal clearance of digoxin.

The potential for telithromycin to inhibit the CYP3A4 pathway is comparable with clarithromycin even though metabolism of telithromycin does not result in the formation of nitrosalkalene metabolite [11]. Telithromycin also competitively inhibits the CYP2D6 system. Limited published data are available on potential drug interactions with telithromycin. No significant interactions seem to occur with warfarin, paroxetine, magnesium hydroxide, aluminum hydroxide, and ranitidine. Telithromycin, however, results in increases in the AUC values of the following drugs: cisapride (2.4-fold); theophylline (1.2-fold); digoxin (1.4-fold); simvastatin (8.9-fold); and midazolam (sixfold) [11]. Caution should be used administering telithromycin with other drugs metabolized by the CYP3A4 enzymes.

## Summary

The advanced macrolides (azithromycin and clarithromycin) and ketolides (telithromycin) are structural analogues of erythromycin that have similar mechanisms of action. These antimicrobials have several distinct advantages over erythromycin including the following: improved oral bioavailability, longer half-life allowing once- or twice-daily administration, higher tissue concentrations, enhanced antimicrobial activity, and less gastrointestinal adverse effects. Clarithromycin and azithromycin have been used extensively for the treatment of upper and lower respiratory tract infections and shown to have similar clinical efficacy to many other antimicrobials. Despite the increasing prevalence of macrolide resistance among *S pneumoniae*, clinical failures have been infrequently reported. 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 for preventing and treating disseminated *M avium* complex infections in HIV-infected patients.

Telithromycin has been shown to be effective clinically in the treatment of outpatient respiratory diseases. Theoretically, telithromycin has an advantage over the macrolides because it remains active in vitro against most macrolide-resistant *S pneumoniae* isolates. Further studies are needed to prove whether this translates into a clinical advantage for the treatment of

respiratory tract infections. Telithromycin is expected to receive final FDA approval for clinical use in the treatment of sinusitis, AECB, and CAP.

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