

KUCERS' THE USE OF ANTIBIOTICS

A CLINICAL REVIEW OF ANTIBACTERIAL, ANTIFUNGAL, ANTIPARASITIC AND ANTIVIRAL DRUGS

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Azithromycin

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I. DESCRIPTION

Azithromycin (CAS number: 83905-01-5) was obtained by Beckman rearrangement of the oxime derivative of the ketone of erythromycin (see Chapter 59, Erythromycin), leading to a 15-membered macrocycle, followed by its reduction and N-alkylation (hence the name of azalide given to this class of compounds (Djokic *et al.*, 1987; Bright *et al.*, 1988). The molecular formula is $C_{38}H_{72}N_2O_{12}$ and the molecular weight is 749; the structure is shown in Figure 62.1.

Azithromycin has greater *in vitro* activity than erythromycin against some Gram-negative bacteria and improved pharmacokinetics with a

relatively long half-life (Dunkin *et al.*, 1988; Maskell *et al.*, 1990). It accumulates significantly intracellularly. It also shows activity against nontuberculous mycobacteria, including *Mycobacterium avium* complex (MAC) (Watt *et al.*, 1996a), and some parasites, such as *Toxoplasma gondii* (Araujo *et al.*, 1988). Apart from its use as an antimicrobial agent, it is increasingly used as an anti-inflammatory agent, in particular in patients with cystic fibrosis.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Macrolides are bacteriostatic antibiotics, characterized by a moderately broad spectrum of activity, which includes most Gram-positive but only selected Gram-negative organisms, as well as several bacteria responsible for intracellular infection, such as *Mycobacteria* spp., *Chlamydia* spp., or *Legionella* spp. Their activity is markedly reduced in acidic environments. Table 62.1 lists the susceptibilities observed for wild strains of the most relevant target organisms.

Gram-positive bacteria

Similar to erythromycin (see Chapter 59, Erythromycin), azithromycin is active against erythromycin-susceptible strains of *Streptococcus*

pyogenes, group B, C and G streptococci, *S. pneumoniae*, *S. viridans*, *S. bovis*, *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus faecalis*, and *E. faecium*. *Listeria monocytogenes* is also moderately susceptible (Seral *et al.*, 2003b). Azithromycin MICs are similar to or slightly higher than those of erythromycin against these organisms.

Gram-positive anaerobic cocci such as the *Peptostreptococcus* spp. are also azithromycin susceptible. The same is true for Gram-positive anaerobic rods, such as *Clostridium*, *Actinomyces*, *Propionibacterium*, *Eubacterium*, *Lactobacillus* spp., and *Corynebacterium diphtheriae* (Barry *et al.*, 1988; Maskell *et al.*, 1990; Williams *et al.*, 1992; Engler *et al.*, 2001).

Gram-negative bacteria

Overall, azithromycin is more active than erythromycin toward Gram-negative bacteria, probably because of a high penetration inside these bacteria due to its higher lipophilicity and/or cationic character (Farmer *et al.*, 1992; Vaara, 1993).

Azithromycin is more active against *Neisseria meningitidis* and *N. gonorrhoeae* than erythromycin (Barry *et al.*, 1988; Slaney *et al.*, 1990). *Haemophilus influenzae* and *Moraxella catarrhalis* are some 4-fold more susceptible to azithromycin than to erythromycin and clarithromycin (Barry *et al.*, 1988; Maskell *et al.*, 1990; Barry and Fuchs, 1995; Zhanet *et al.*, 2003a). *H. ducreyi* is also more susceptible to azithromycin than erythromycin (Slaney *et al.*, 1990; Aldridge *et al.*, 1993; Jonas *et al.*, 2000). Azithromycin is about as active as erythromycin against *Legionella pneumophila* and *L. micdadei* *in vitro*, but more active against these pathogens intracellularly (Edelstein and Edelstein, 1991; Donowitz and Earnhardt, 1993). *Campylobacter jejuni* and *C. coli* are about as susceptible to azithromycin as to erythromycin (Taylor and Chang, 1991).

Unlike erythromycin, azithromycin is active against some of the Enterobacteriaceae, particularly the enteropathogens, such as enteropathogenic *Escherichia coli* and the *Shigella* and *Salmonella* spp. Azithromycin is particularly effective against these pathogens intracellularly (Retsema *et al.*, 1987; Gordillo *et al.*, 1993; Rakita *et al.*, 1994). It also has some activity against other *E. coli* strains, *Y. enterocolitica*, *Leclercia adecarboxylata*, *Plesiomonas shigelloides*, and *C. diversus* (Stock and Wiedemann, 2001; Stock *et al.*, 2004). *Kluyvera*

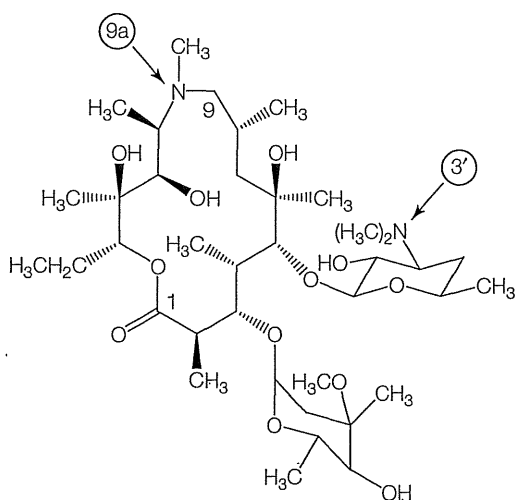


Figure 62.1 Molecular structure of azithromycin. Chemical stability in acid medium is due to absence of a keto group in position 9. Note that azithromycin is built on a 14-membered cycle and is a diaminated compound (Djokic *et al.*, 1987).

Table 62.1 MIC ($\mu\text{g/ml}$) of azithromycin for target bacteria compared with susceptibility breakpoints.

Bacteria	Wild-type strains (EUCAST distributions of MIC)			Study period	Clinical isolates			Breakpoints		Resistance issues	References
	Range	MIC ₅₀	MIC ₉₀		Range	MIC ₅₀	MIC ₉₀	CLSI breakpoint (S \leq /R \geq)	EUCAST breakpoint (S \leq /R \geq)		
<i>Staphylococcus aureus</i>	0.032–2	0.5	1	1994–1998 (Japan)	0.5 to >128		>32	2/8	1/2	HA-MRSA frequently multiresistant	Okamoto <i>et al.</i> , 2000
<i>Streptococcus pneumoniae</i>	0.032–0.25	0.125	0.125	1994–2001	≤ 0.016 to >64			0.5/2	0.25/0.5	High prevalence in many countries; often multiresistant strains	Kosowska <i>et al.</i> , 2005
<i>Streptococcus pyogenes</i>	0.032–0.25	0.064	0.25	2002–2003 (Japan) 1999–2000 (Europe) 1994–1998 (Japan)	≤ 0.06 to >16	4	16	0.5/2	0.25/0.5		Sunakawa and Farrell, 2007 Canton <i>et al.</i> , 2002
<i>Haemophilus influenzae</i>	0.064–4	1	2	2007 (Spain)	0.5–8	2	4	4/–	0.12/4		Garcia-Cobos <i>et al.</i> , 2008
<i>Moraxella catarrhalis</i>				1997–2002 (Canada)	≤ 0.06 –2	0.06	0.12		0.5/0.5		Zhanet <i>et al.</i> , 2003b
<i>Legionella pneumophila</i>				1999–2004 (Europe, USA)	≤ 0.06 –0.5	≤ 0.06	0.25				Dunbar and Farrell, 2007
<i>Chlamydia trachomatis</i>				1997–1999 (Israel)	0.06–0.125	0.06	0.125				Samra <i>et al.</i> , 2001
<i>Neisseria gonorrhoeae</i>	0.016–0.25	0.125	0.25		0.016–0.25	0.064	0.19		0.25/0.5		Khaki <i>et al.</i> , 2007
<i>Mycobacterium avium</i> and complex				(UK)	<8–64	32	32				Watt <i>et al.</i> , 1996a

CLSI: Clinical Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; HA-MRSA: hospital acquired methicillin-resistant *S. aureus*; R: resistance; S: susceptibility.

ascorbata is less susceptible than *K. cryocrescens* (Stock, 2005). *Klebsiella* and *Enterobacter* spp. and *C. freundii* are more resistant and the *Proteus* and *Serratia* spp. and *Y. pestis* are completely resistant (Retsema *et al.*, 1987; Smith *et al.*, 1995).

Azithromycin is more active than erythromycin against *Brucella* spp. with MICs of 0.5–2.0 µg/ml (Landinez *et al.*, 1992; Garcia-Rodriguez *et al.*, 1993) and *Vibrio cholerae*, with an MIC of 0.25 µg/ml (Jones *et al.*, 1988). Azithromycin also shows some activity against other Gram-negative bacteria such as the *Bartonella* spp., *Cardiobacterium hominis*, and the *Pasteurella*, *Aeromonas* and *Acinetobacter* spp., but *Pseudomonas aeruginosa* is completely resistant (Retsema *et al.*, 1987; Kitzis *et al.*, 1990; Lion *et al.*, 2006; Timurkaynak *et al.*, 2006). Azithromycin is ineffective against *Coxiella burnetii* (Lever *et al.*, 2004). Only a small minority of *Burkholderia pseudomallei* are sensitive to azithromycin (Karaunakaran and Puthuchear, 2007).

Among the Gram-negative anaerobic bacteria, the *Prevotella* spp., *Porphyromonas* spp., *Fusobacterium* spp., *Actinobacillus actinomycetem-comitans*, *Peptostreptococcus micros*, and *Eikenella corrodens* are azithromycin-susceptible (Muller *et al.*, 2002; Kuriyama *et al.*, 2007). *Veillonella* spp., *Bacteroides fragilis*, and other members of the *B. fragilis* group are moderately resistant (Barry *et al.*, 1988; Kitzis *et al.*, 1990; Chen *et al.*, 1992; Pajukanta *et al.*, 1992).

Other bacteria

Azithromycin is active against MAC, with MICs similar or slightly higher than those of clarithromycin (Bermudez and Young, 1988; Perronne *et al.*, 1991). It is also as active as clarithromycin (see Chapter 61, Clarithromycin) against other nontuberculous mycobacteria, such as *M. kansasii*, *M. xenopi*, *M. simiae*, *M. malmoense*, and *M. celatum* (Klemens and Cynamon, 1994; Fattorini *et al.*, 2000). *M. marinum* is resistant to azithromycin; however, clarithromycin has moderate activity (Aubry *et al.*, 2000).

Azithromycin is highly active against *Mycoplasma pneumoniae* (Ishida *et al.*, 1994), and *Chlamydia trachomatis*, *Chlamydia pneumoniae*, or *C. psittaci* (Walsh *et al.*, 1987; Hammerschlag *et al.*,

1992; Niki *et al.*, 1994). It also demonstrated activity *in vitro* or in animal models of infection by *Ureaplasma urealyticum* (Rylander and Hallander, 1988), *Treponema pallidum* (Lukehart *et al.*, 1990), *Borrelia burgdorferi* (Johnson *et al.*, 1990; Hunfield *et al.*, 2004), or *T. gondii* (Araujo *et al.*, 1988). Azithromycin and clarithromycin are equally active against leptospira (Ressner *et al.*, 2008). Azithromycin also has some *in vitro* activity against *Cryptosporidium parvum* in cell lines (Rehg, 1991; Giacometti *et al.*, 2000); however, there have been concerns about clinical efficacy (Giacometti *et al.*, 1999). Azithromycin has antimalarial activity on its own, as well as synergistic interactions with artemisinin derivatives or quinine (Gingras and Jensen, 1992; Noedl *et al.*, 2007). *Ehrlichia phagocytophila* is uniformly resistant to azithromycin using standardized sensitivity testing with cell cultures (Horowitz *et al.*, 2001).

2b. Emerging resistance and cross-resistance

Resistance to macrolides has become a major issue for most of the bacteria originally described as susceptible, including among *Staphylococcus* spp., *Streptococcus* spp., *N. gonorrhoeae*, *Bacteroides* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Lactobacillus* spp., *M. pneumoniae*, *M. genitalium*, *Campylobacter* spp., *C. diphtheriae*, and *Propionibacterium*, as well as many members of the Enterobacteriaceae (Leclercq and Courvalin, 1991; Engler *et al.*, 2001; Martin *et al.*, 2006; Jensen *et al.*, 2008). There is complete cross-resistance between erythromycin and roxithromycin. The main mechanisms of resistance are similar to erythromycin and include target modification, antibiotic inactivation and efflux mechanisms (see Chapter 59, Erythromycin).

Because of its use as an immunomodulatory agent, the drug has been given for prolonged periods of time to cystic fibrosis patients. Phaff *et al.* (2005) showed that long-term use of azithromycin led to increased resistance of *S. aureus* and *H. influenzae*, and thereby decreasing its potential use as an antimicrobial.

3. MECHANISM OF DRUG ACTION

The mechanism of action is similar to erythromycin (see Chapter 59, Erythromycin).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

Oral administration

Azithromycin is mainly given by the oral route. The adult dose for most indications is 500 mg once daily on the first day and 250 mg once daily for the next 4 days, or, alternatively, 500 mg once daily for only 3 days (Foulds *et al.*, 1990; Foulds and Johnson, 1993). The shortness of treatment duration with azithromycin is made possible by its particular pharmacokinetic profile (high and persistent tissue concentrations; see below under 5. Pharmacokinetic and pharmacodynamic features) (Klein, 1994). For specific indications, however, other dosages are used.

For MAC, the dosage is 1200 mg once weekly for primary prevention, or 500 mg daily (combined with ethambutol or rifampicin) for the secondary prevention in immunocompromised patients (Benson, 1994), and 600 mg daily in combination with other antimycobacterial agents for the treatment of disseminated infection, or 500–600 mg three times a week or 300 mg daily for the treatment of lung disease (Griffith *et al.*, 2007). For the treatment of sexually transmitted diseases, a single dose of 1 g (to 2 g for cervicitis or

urethritis due to *N. gonorrhoeae*) is recommended (Steingrimsson *et al.*, 1994; Workowski and Berman, 2006).

A daily dose of 500 mg, but for a longer period of time, is administered for typhoid fever (7 days) or acute toxoplasmic encephalitis in AIDS patients (4 weeks) (Saba *et al.*, 1993; Girgis *et al.*, 1999).

An extended-release formulation has recently been developed, allowing for use of a single 2-g dose in respiratory tract infections (Swainston and Keam, 2007).

Parenteral administration

Azithromycin can be administered by the intravenous route. The powder is first reconstituted at a concentration of 100 mg/ml (it cannot be used for intramuscular or for bolus injection), and is further diluted to 1 mg/ml for an administration over 3 hours or to 2 mg/ml for an administration over 1 hour (Luke and Foulds, 1997).

Other routes of administration

A 1% ophthalmic suspension is available for topical use only.

4b. Newborn infants and children

The dosage for children age six months or older is 10 mg/kg as a single dose on day 1 followed by 5 mg/kg once daily for the next 4 days, or, alternatively 10 mg/kg once daily for 3 days only (Hamill, 1993; Nahata *et al.*, 1993; Schaad, 1993). In otitis media, a single dose of 30 mg/kg has also been approved. For disseminated infection by *M. avium*, a daily dose of 10–12 mg/kg azithromycin (combined with antimycobacterial agents) is recommended. For typhoid fever, 20 mg/kg/day for 5 days or 10 mg/kg/day for 7 days have been used successfully (Frenck *et al.*, 2000; Frenck *et al.*, 2004). The extended release formulation should be administered as a single dose of 60 mg/kg in children older than six months.

4c. Altered dosages

Impaired renal function

No dosage adjustment is required in patients with a glomerular filtration rate of ≤ 80 ml/min (Hoffler *et al.*, 1995), but azithromycin

should be used with caution when this rate becomes lower than 10 ml/min. Most guidelines do not recommend dose adjustment in renal impairment (Aronoff *et al.*, 1999; Gilbert *et al.*, 2008). Dose reduction is not necessary for patients on hemodialysis, continuous ambulatory peritoneal dialysis or continuous arteriovenous hemofiltration (Aronoff *et al.*, 1999).

Impaired hepatic function

A study with 16 cirrhotic patients with moderate hepatic impairment (Pugh's class A and B) suggested that no modification of azithromycin dosage is necessary for short-course treatment (Mazzei *et al.*, 1993).

The elderly

No dosage adjustment is needed for geriatric patients, as pharmacokinetic parameters, efficacy, and toxicity measures are similar to younger populations.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

The main pharmacokinetic properties of azithromycin are summarized in Table 62.2.

5a. Bioavailability

After a single 500 mg oral dose of azithromycin, a mean peak serum level of 0.4 μ g/ml was reached in 2–4 hours. The serum levels in children are similar to those in adults if they are given a single dose of azithromycin 10 mg/kg on day 1 and 5 mg/kg daily for the next 4 days (Nahata *et al.*, 1993). The oral bioavailability of azithromycin is 38%. The AUC of azithromycin was unaffected by food intake (but C_{max} is increased by 56%) and by the co-administration of antacids or of cimetidine.

After administration of a single dose of 2 g of the extended-release formulation, serum C_{max} and AUC_{24h} are 3- to 4-fold higher than with a conventional dose of 500 mg of the immediate release formulation, with serum concentrations remaining > 1 μ g/ml for 120 hours, as was the case after a conventional 3 days' treatment (Ehnage *et al.*, 2008). The extended release formulation shows an improved bioavailability (83%) compared with the conventional formulation. It is best absorbed when taken on an empty stomach and can be co-administered with antacids (Chandra *et al.*, 2007).

5b. Drug distribution

After reaching the C_{max} , the serum level of azithromycin thereafter declines to 0.1 μ g/ml at 6 hours and 0.04 μ g/ml at 12 hours. This initial

rather rapid fall of serum levels is not due to the drug's elimination, but is due to extensive uptake of azithromycin in the tissues.

Probably the most striking pharmacokinetic property of azithromycin is its large volume of distribution, which is related to its exceptional ability to accumulate inside eukaryotic cells. This can be ascribed to the fact that azithromycin possesses two portonable amine functions, responsible for a higher retention in the acidic compartments of the cells than for the other, monocationic macrolides (de Duve *et al.*, 1974; Carlier *et al.*, 1994). The consequences of this large volume of distribution is that the serum level of azithromycin is low, which may limit its efficacy, whereas its tissue and cellular concentrations are high, which may be an advantage for the treatment of infections localized in these compartments (Schentag and Ballow, 1991; Zhanel *et al.*, 2001). Thus, in animal models, tissue-serum concentrations as high as 100-fold have been found in spleen, liver, kidneys, lung, lymph nodes, and tonsils, 20-fold in the eye, 10-fold in muscle and fat, but only 1.2-fold higher in the brain (Shepard and Falkner, 1990; Davila *et al.*, 1991; Carceles *et al.*, 2007). This high tissue concentration has been correlated with efficacy in models of infections by *S. pyogenes*, *S. pneumoniae*, group B streptococci, and *H. influenzae* (Girard *et al.*, 1987; Tissi *et al.*, 1995). Its high cellular concentration has been correlated with its high activity against intracellular pathogens, including *L. pneumophila* (Stamler *et al.*, 1994), *C. trachomatis* (Raulston, 1994), *M. avium* (Bermudez *et al.*, 1991), and *T. gondii* (Blais *et al.*, 1994; Schwab *et al.*, 1994). However, it is poorly effective in experimental *S. aureus* osteomyelitis (O'Reilly *et al.*, 1992), despite bone concentrations 30 times higher than levels in the serum (Foulds *et al.*, 1990; O'Reilly *et al.*, 1992), as well as against *S. aureus* ingested by polymorphonuclear neutrophils (PMNs), or macrophages (Meyer *et al.*, 1993; Pascual *et al.*, 1995; Seral *et al.*, 2003a; Barcia-Macay *et al.*, 2006). This could be ascribed to the fact that *S. aureus* is localized in phagolysosomes, where this acidic pH drastically impairs the activity of azithromycin (Seral *et al.*, 2003a; Barcia-Macay *et al.*, 2006).

In humans also, a broad tissue distribution has been demonstrated, with tissue concentrations after administration of 500 mg of 0.4–5.1 μ g/g in tonsillar tissue even after 1 week (Schmedes *et al.*, 1998), of 9 μ g/g in the lung (Danesi *et al.*, 2003), giving rise to tissue-concentration ration > 100 in the lung and the tonsil, 70 in the cervix, and 30 in the sputum or in the skin. It is still more effective with the extended release formulation. Thus, after administration of a single 2-g dose of the extended-release formulation, the maximal concentration was reached after 16–24 hours in the sinus, the lung or the alveolar macrophages, and after 48 hours in the epithelial lining fluid; however

Table 62.2 Pharmacokinetic parameters of azithromycin.

Pharmacokinetic parameter	Azithromycin (500 mg, 2 days)	Extended release (2 g)
C_{max} (μ g/ml)	0.4	~1
t_{max} (hours)	2.5	4
$t_{1/2}$ (hours)	72	59
Bioavailability (%)	37	83
Protein binding (%)	12–40	
Tissue serum concentration	50–1150	
AUC (mg/h) 24 h	2–3.4	7–10

Compiled from Foulds *et al.* (1990); Peters *et al.* (1992); Chandra *et al.* (2007); Ehnage *et al.* (2008); Lucchi *et al.* (2008).

the AUC was three to four times higher than with the conventional treatment and about four to five times higher in the sinus and in the epithelial lining fluid, and seven times higher in the lung or the alveolar macrophages than in the serum (Ehnhage *et al.*, 2008; Lucchi *et al.*, 2008).

In pregnancy, there is limited transplacental transfer of azithromycin; mean placental transfer was 2.6%, a ratio between the steady state concentrations in fetal venous and maternal arterial circulations (Heikkinen *et al.*, 2000). However, azithromycin has a rapid serum half-life in term gravid women with a prolonged tissue half-life (levels sustained for up to 72 hours) and high sustained antibiotic levels within the myometrium, adipose, and placental tissue (Ramsey *et al.*, 2003).

In animal models, tissue serum concentrations of azithromycin are 1.2-fold higher in the brain (Davila *et al.*, 1991).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Cure rates for macrolides mainly depend on the AUC/MIC ratio (Andes *et al.*, 2004), based on their time-dependent effect coupled with a postantibiotic effect, both *in vitro* and in animal models (Rolin and Bouanchaud, 1989; Novelli *et al.*, 2002). Girard *et al.* (2005) also showed the AUC/MIC ratio as the most important pharmacodynamic index correlated with efficacy in a mouse model of infection.

The pharmacodynamic activity of azithromycin against macrolide-susceptible and -resistant *S. pneumoniae* was examined *in vitro* by simulating clinically achievable free serum, epithelial lining fluid (ELF), and middle ear fluid concentrations in their models, leading to the conclusion that a free azithromycin AUC/MIC of ≥ 36.7 allows for a bactericidal effect against a macrolide-susceptible *S. pneumoniae* with an MIC of ≤ 0.05 $\mu\text{g/mL}$ (Zhan *et al.*, 2003a). In bacteremic patients with pneumococcal infections, it was shown that azithromycin AUC/MIC averaged ten in failure patients and 17 in controls (Schentag *et al.*, 2007), suggesting a pharmacodynamic breakpoint of 0.2 $\mu\text{g/ml}$ based on an AUC of ~ 3 mg/h. This is in the order of magnitude of the European Committee on Antimicrobial Susceptibility Testing breakpoint for resistance (0.5 $\mu\text{g/ml}$), but is well below the Clinical Laboratory Standards Institute breakpoint (2 $\mu\text{g/ml}$).

However, it is important to remember that azithromycin is highly concentrated within the host cells. It may therefore have a more favorable pharmacodynamic profile toward intracellular bacteria. Moreover, concentrations in human PMNs after conventional treatments peak to ~ 120 $\mu\text{g/ml}$ and remain above 60 $\mu\text{g/ml}$ 7 days after the final dose, and the concentration is about twice as high in inflamed as noninflamed blister fluid (Ballou *et al.*, 1998), which has led some to propose a role for PMNs in the delivery of azithromycin at the site of infection (Schentag and Ballou, 1991).

With respect to other routes of administration, once-daily instillation of 1.0% eye drops was shown to reach an AUC/MIC above the required threshold for antibacterial activity against Gram-positive bacteria (25–35). A twice-daily instillation is likely to ensure antimicrobial activity against Gram-negative bacteria (threshold > 100) (Chiambaretta *et al.*, 2008).

5d. Excretion

Owing to its high cellular retention, the elimination of azithromycin is extremely slow. The drug is still detected in the serum 3 weeks after its administration, with concentrations > 1 $\mu\text{g/l}$ during 15–30 days (Crokaert *et al.*, 1998). The persistence of subinhibitory concentrations in the serum raises potential questions regarding the potential for selection of resistance.

Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Only 4–6% of an orally administered

dose of azithromycin is excreted via the kidney as the active drug (Cooper *et al.*, 1990; Wildfeuer *et al.*, 1993).

5e. Drug interactions

Drug interactions with macrolides can be a considerable problem, which may seriously limit their use in at-risk patients. The main mechanism involved in these interactions is the ability of macrolides to bind to cytochrome P450 (group 3A4), thereby impairing the subsequent metabolism of other substrates of the same cytochrome (Periti *et al.*, 1992). The elimination of these co-administered drugs is therefore reduced, causing a potential risk of toxicity (Periti *et al.*, 1992; von Rosensteil and Adam, 1995). This risk, however, is the lowest with azithromycin, so that its use is contraindicated only when the interaction may have a life-threatening risk (see Table 62.3) (Pai *et al.*, 2000). This is the case for ergotamine (risk of ergotism) or for drugs that result in prolongation of the cardiac QT interval (e.g. terfenadine), thereby increasing the risk of torsades de pointes due to the macrolides (Curtis *et al.*, 2003). Among the newer antihistamines, peak fexofenadine concentrations were increased by 67% in the presence of azithromycin, whereas the desloratidine and azithromycin combination was better tolerated with only a small ($< 15\%$) increase in mean pharmacokinetics (Gupta *et al.*, 2001). However, both antihistamines in combination with azithromycin did not significantly alter the electrocardiogram. Azithromycin does not significantly alter the pharmacokinetics of rupatadine, an oral antihistamine and platelet-activating factor antagonist (Solans *et al.*, 2008).

Azithromycin is also described as an inhibitor and a substrate of P-glycoprotein, which may explain how it increases the serum level of ciclosporin (Page *et al.*, 2001) or digoxin (Eberl *et al.*, 2007). Conversely, nelfinavir increases the serum concentration and AUC of azithromycin probably by inhibiting its transport by P-glycoprotein in the gut (Amsden *et al.*, 2000), justifying a close monitoring for known azithromycin side-effects, such as liver enzyme abnormalities and hearing impairment.

Azithromycin potentially interacted with ciclosporin to increase ciclosporin levels in a case report; however, two follow-up studies of a total of 14 renal transplant patients did not show an interaction (Ljutić and Rumboldt, 1995; Gomez *et al.*, 1996; Bachmann *et al.*, 2003). There has been a case report of a marked increase in tacrolimus blood levels after two doses of azithromycin (Mori *et al.*, 2005). Tacrolimus undergoes extensive cytochrome P450 (CYP) 3A4 metabolism, and, although azithromycin has minimal effects on CYP, there may be an interaction between the two drugs.

Similar to other macrolides, azithromycin is thought to eliminate *Eubacterium lentum*, which can inactivate up to 40% of intestinal digoxin (Pai *et al.*, 2000). A case series of two patients with elevated digoxin concentrations with co-administration with azithromycin has been reported (Thalhammer *et al.*, 1998).

Table 62.3 Drug interactions with azithromycin.

Contraindicated drugs (careful monitoring required)	Drugs increasing azithromycin concentrations
Digoxin	Nelfinavir
Disopyramide	
Ergotamine or dihydroergotamine	
Tacrolimus	
Terfenadine	
Ciclosporin	
Hexobarbital	
Lovastatin	
Melegreatan	
Phenytoin	
Rifampicin	
Warfarin	

Compiled from www.drugbank.ca/drugs/DB00207.

Although co-administration of rifabutin and azithromycin has not been shown to alter the pharmacokinetics of either drug, the combination increases the risk of severe neutropenia. A controlled study comparing the effects of clarithromycin and azithromycin on the pharmacokinetics of rifabutin involving 30 healthy volunteers was terminated after neutropenia developed in 14 participants (Apseloff *et al.*, 1998). The incidence of neutropenia was greater in the combination group than in patients solely receiving rifabutin. The combination of azithromycin and rifabutin should be used cautiously with close monitoring for neutropenia.

Owing to the lack of cytochrome P450 interactions, azithromycin is considered to be the macrolide of choice for patients taking warfarin. However, there are at least seven case reports suggesting an azithromycin-warfarin interaction with resultant increase in international normalized ratio. However, confounding variables existed in each of the cases, including hepatic dysfunction, poor appetite, and concomitant medications (Lane, 1996; Woldtved *et al.*, 1998; Foster and Milan, 1999; Wiese and Cosh, 1999; Williams and Ponte, 2003; Shrader *et al.*, 2004). In a recent case report, a decrease in cigarette smoking from 1 pack/day to 1 pack every 3 days was the only confounding variable (Shrader *et al.*, 2004). In contrast, a retrospective review of 52 cases did not demonstrate a drug interaction (Beckey *et al.*, 2000). The accumulating case reports suggest that clinicians should be mindful of a potential warfarin-azithromycin interaction.

6. TOXICITY

Azithromycin is well tolerated with few side-effects, although the use of higher doses may be associated with greater toxicity. For instance, high-dose azithromycin (600 mg daily) used in mycobacterial infections is associated with 82% patients experiencing gastrointestinal disorders, 2% hearing impairment, tinnitus in 46%, and poor balance or dizziness in 28% (Brown *et al.*, 1997); adverse effects were generally associated with higher serum concentrations.

6a. Gastrointestinal adverse effects

These are the most common side-effects and easily observed by patients (Periti *et al.*, 1993; Treadway *et al.*, 2002), with diarrhea/loose stools (4–5%), nausea (3%), and abdominal pain (2–3%) being the most frequently reported. With the extended release formulation (2 g azithromycin), the reported rates are 17% nausea, 18% diarrhea/loose stools, 4% vomiting, and 36% abdominal pain (Chandra *et al.*, 2007). The incidence of gastrointestinal reactions is lower with azithromycin than that reported with erythromycin (Periti *et al.*, 1993). The mechanism for the gastrointestinal effects is macrolide-induced endogenous release of motilin that stimulates motilin receptors and has a prokinetic effect on the gut (Catnach and Fairclough, 1992).

6b. Hepatotoxicity

Transaminase elevation may occur upon treatment in 7% of patients but it is reversible upon completion of the therapy (Vergis *et al.*, 2000). Rare cases of more severe reactions (e.g. intrahepatic cholestasis and hypersensitivity hepatitis) have been reported (Longo *et al.*, 1997; Cascaval and Lancaster, 2001; Chandrupatla *et al.*, 2002).

6c. Cardiac effects

Macrolides have been associated with prolongation of cardiac repolarization (prolongation of the QT interval). The molecular mechanism appears to be a blockade of the HERG channel-dependent potassium current in myocyte membranes (Roden, 2008). These interactions may give rise to polymorphic ventricular tachycardia, torsades de pointes, or ventricular fibrillation. In a rat model, the

Two cases of rhabdomyolysis have occurred with co-administration of lovastatin, a hydroxymethylglutaryl-coenzyme A reductase inhibitor, and clarithromycin and azithromycin. Both cases had been treated for over five years with lovastatin, and the development of rhabdomyolysis coincided with co-administration with the macrolides (Grunden and Fisher, 1997). "Statin" monotherapy is known to cause rhabdomyolysis and rhabdomyolysis with the newer macrolides may occur when co-administered with other "statins".

Azithromycin has been reported to cause disopyramide toxicity with ventricular arrhythmias, presumably by inhibiting dealkylation of disopyramide to its major metabolite mono-*N*-dealkyldisopyramide (Grañowitz *et al.*, 2000).

Azithromycin increased the exposure of melagatran, the active form of the oral direct thrombin inhibitor ximelagatran, although the activated partial thromboplastin time (APTT) was not significantly altered (Dorani *et al.*, 2007).

Azithromycin has not been shown to significantly interact with carbamazepine, cimetidine, didanosine, indinavir, zidovudine, sildenafil, theophylline, zafirlukast, ciapride, and midazolam (Foulds *et al.*, 1991; Rapeport *et al.*, 1991; Chave *et al.*, 1992; Foulds *et al.*, 1999; Garey *et al.*, 1999; Michalets and Williams, 2000; Pai *et al.*, 2000; Muirhead *et al.*, 2002; Ito *et al.*, 2003).

potency of macrolides to induce QTc prolongation was ranked as follows: erythromycin > clarithromycin > roxithromycin > azithromycin (Ohtani *et al.*, 2000). Rare cases of QTc interval prolongation (Matsunaga *et al.*, 2003; Russo *et al.*, 2006), sometimes leading to torsades de pointes, have been reported (Huang *et al.*, 2007; Kezerashvili *et al.*, 2007).

6d. Ototoxicity

Reversible ototoxicity is reported in patients receiving long-term therapy for *M. avium* infection and 8 days of intravenous azithromycin for pneumonia (Wallace *et al.*, 1994; Bizjak *et al.*, 1999). Clinicians should be aware that irreversible hearing loss has also been reported with low-dose oral azithromycin for a urinary tract infection (Ross and Gross, 2000). There have also been case reports of ototoxicity occurring in patients with HIV (Tseng *et al.*, 1997). Guinea-pig models have shown reversible reductions in transiently evoked otoacoustic emissions with clarithromycin and azithromycin, but not erythromycin (Uzun *et al.*, 2001). The authors attribute this to transient dysfunction of outer hair cells in the inner ear.

6e. Hypersensitivity reactions

Allergic reactions including eosinophilia, fever, and skin eruptions are rarely reported for macrolides (Periti *et al.*, 1993; Taylor *et al.*, 2003); but when they occur they usually resolve promptly with treatment cessation. In a small case series, four of 21 pharmaceutical workers exposed to powdered substances involved in azithromycin synthesis developed allergic contact dermatitis with positive patch testing (Milkovic-Kraus *et al.*, 2007).

6f. Other adverse reactions

Headache is commonly reported (1.3%) in patients taking 2 g of extended release formulation. Transient neutrophilia (1.5%) and neutropaenia (1.5%) has been documented (Hopkins, 1996). There is one report of severe exacerbation of *Myasthenia gravis* with azithromycin treatment (Cadisch *et al.*, 1996).

There have been case reports of azithromycin causing acute interstitial nephritis. An adult developed end-stage renal failure after receiving azithromycin for 9 days (Mansoor *et al.*, 1993). A 14-year-old child developed recurrent acute interstitial nephritis induced by azithromycin administration (Soni *et al.*, 2004).

A syndrome similar to Churg–Strauss with eosinophilia, arthralgia, fever and rash has occurred in a patient who received azithromycin and roxithromycin on separate occasions (Hubner *et al.*, 1997).

6g. Risk in pregnancy

Azithromycin belongs to the B category of risk in pregnancy; there is not enough clinical experience in pregnancy to confirm its safety, although animal studies have recently suggested teratogenicity. In rat

embryo models, macrolides significantly decreased all growth and developmental parameters dose dependently compared with controls (Karabulut *et al.*, 2008). Clarithromycin caused more developmental toxicity, whereas azithromycin had more teratogenicity potential and spiramycin had the lowest toxic and teratogenic effects observed. Two observational studies have suggested that gestational exposure to azithromycin is not associated with an increased risk of congenital malformations; however, study sizes were small (Sarkar *et al.*, 2006; Bar-Oz *et al.*, 2008). Although in pregnancy azithromycin has a rapid serum half-life and limited placental transfer (see above under 5b. Drug distribution), sustained high levels are obtained within myometrium, adipose, and placental tissue. This is consistent with animal and observational studies, and azithromycin should be used with caution during pregnancy.

7. CLINICAL USES OF THE DRUG

A key therapeutic benefit with azithromycin is its easy scheme of administration. Azithromycin has a number of indications, particularly in respiratory tract infections. Macrolides have long been considered an alternative to beta-lactams for the treatment of respiratory tract infections. Short courses of azithromycin are as effective as longer courses of other antibiotics for upper and lower respiratory tract infections (Cantopoulos-Ioannidis *et al.*, 2001; Ionnidis *et al.*, 2001). However, the increasing rate of resistance among many respiratory pathogens to macrolides (see Section 2b. Emerging resistance and cross-resistance) requires some caution when prescribing, such that macrolide usage for these indications should be limited to countries where resistance rates remain low (Brunton and Iannini, 2005; Lode, 2007).

7a. Upper respiratory tract infections

Azithromycin is proposed as a second-line therapy for tonsillopharyngitis. Recently, it was suggested that azithromycin (10 mg/kg/day for 3 days for 3 successive weeks) may be considered for symptomatic treatment in the eradication of atypical organisms (*M. pneumoniae* and *C. pneumoniae*) that can be found in children with acute tonsillopharyngitis who are at high risk of recurrence of respiratory illness (Esposito *et al.*, 2006).

Azithromycin is indicated in the treatment of acute otitis media (in children) and acute sinusitis caused by *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

Acute otitis media

Multiple clinical trials in pediatric patients with acute otitis media (AOM) have demonstrated that 3- and 5-day courses of azithromycin are safe and have similar clinical efficacy to other agents commonly used as a 10-day regime (Arguedas *et al.*, 1996; Khurana, 1996; McLinn, 1996; Arguedas *et al.*, 1997). Single-dose azithromycin therapy (30 mg/kg) is an alternative to short-course azithromycin or high-dose amoxicillin regimes of longer duration in the treatment of AOM in children, in whom high-level *S. pneumoniae* resistance is uncommon (Arguedas *et al.*, 2003; Block *et al.*, 2003; Dunne *et al.*, 2003; Soley and Arguedas, 2005). A randomized double-blinded study showed that single-dose azithromycin (30 mg/kg) was as effective as high-dose amoxicillin (90 mg/kg in two divided doses) for 10 days in uncomplicated AOM, with lower rates of adverse events (20% and 29%) and improved compliance (Arguedas *et al.*, 2005).

Acute bacterial sinusitis

Azithromycin is an alternative to amoxicillin or amoxicillin–clavulanate for the treatment of acute bacterial sinusitis (Rosenfeld *et al.*,

2007). Short-course azithromycin therapy (500 mg daily) for either 3 or 6 days was as efficacious as a 10-day regime of amoxicillin–clavulanate (500–125 mg three times a day) for clinically and radiologically documented acute bacterial sinusitis in a randomized controlled trial of 936 patients (Henry *et al.*, 2003). Telithromycin (800 mg daily for 5 days) was superior to azithromycin (500 mg daily for 3 days) in the eradication of *S. pneumoniae* from the nasopharynx of adults with acute maxillary sinusitis (Brook and Hausfeld, 2006).

7b. Lower respiratory tract infections

Azithromycin is indicated for acute exacerbations of chronic bronchitis caused by *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* (Amsden *et al.*, 2003; Swanson *et al.*, 2005; Zervos *et al.*, 2007), and of community-acquired pneumonia due to *C. pneumoniae*, *M. pneumoniae*, *L. pneumophila*, *H. influenzae*, or *S. pneumoniae* (Vergis *et al.*, 2000; Feldman *et al.*, 2003; Plouffe *et al.*, 2003).

Acute bronchitis and acute exacerbations of chronic bronchitis

Randomized placebo-controlled trials and subsequent metaanalyses have led to most clinical practice guidelines recommending antibiotics for the treatment of moderate to severe exacerbations (Anthonisen *et al.*, 1987; Bach *et al.*, 2001; Noura *et al.*, 2001; American Thoracic Society/European Respiratory Society Task Force, 2004; Ram *et al.*, 2006). However, there is insufficient evidence to support the use of antibiotic therapy in mild exacerbations (Ram *et al.*, 2006).

A Cochrane meta-analysis was performed to compare azithromycin and amoxicillin or amoxicillin–clavulanate for the treatment of lower respiratory tract infections, including acute bronchitis, acute exacerbations of chronic bronchitis, and pneumonia (Panpanich *et al.*, 2004). The pooled analysis of 14 trials concluded that the incidence of clinical failure on days 10–14 in the azithromycin group and amoxicillin or amoxiclav group was not statistically significantly different in terms of clinical failure, microbial eradication and adverse events, although there were some limitations relating to the quality of the analyzed studies. Adequate concealment of treatment allocations occurred in only three trials, and nearly half had no description of blinding. In patients with acute bronchitis of a suspected bacterial cause, azithromycin tended to be more effective as evidenced by the lower incidence of treatment failure than amoxicillin or amoxiclav. In clinical practice, the choice between azithromycin and amoxicillin or amoxiclav is often based on considerations such as cost, convenience, and compliance to treatment.

Two randomized studies have compared azithromycin and levofloxacin or moxifloxacin in treating acute exacerbations of chronic bronchitis. Azithromycin (500 mg on day 1, followed by 250 mg daily

for days 2–5) was clinically (89% vs 92%) and bacteriologically (96% vs 85%) equivalent to levofloxacin (500 mg daily for 7 days), in 235 outpatients, despite concerns over macrolide resistance and increasing Gram-negative pathogens (Amsden *et al.*, 2003). Five hundred and sixty-seven patients were randomized to receive moxifloxacin (400 mg daily) or azithromycin (500 mg daily for day 1; 250 mg for days 2–5) for 5 days (Deabate *et al.*, 2000). Clinical resolution rates were 88% for moxifloxacin and 86% for azithromycin, with similar bacteriologic eradication rates; 95% for moxifloxacin and 94% for azithromycin; although the *H. influenzae* eradication rate was greater for moxifloxacin.

Azithromycin has more activity against *H. influenzae* than other macrolides (Mandell *et al.*, 2007). However, it should be noted that a dosing regimen of 500 mg initially followed by 250 mg for 4 days was ineffective for eradicating *H. influenzae* from purulent exacerbations of chronic bronchitis (Davies *et al.*, 1989). Compared with other macrolides, a 3-day course of azithromycin is as effective and as well tolerated as a 10-day course of clarithromycin (Bradbury, 1993).

Community-acquired pneumonia

Azithromycin is proposed as first-line therapy of community-acquired pneumonia in previously healthy patients with no risk factors for drug-resistant *S. pneumoniae* by the Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines (Mandell *et al.*, 2007). The presence of comorbidities, such as chronic heart, lung, liver or renal disease, or diabetes mellitus, alcoholism, malignancy, asplenia, immunosuppressing conditions, or use of immunosuppressant drugs, requires the use of either a respiratory fluoroquinolone or a beta-lactam plus azithromycin (Mandell *et al.*, 2007). For those patients requiring admission, including patients requiring intensive care, azithromycin in combination with a beta-lactam, or a respiratory quinolone, is recommended by these IDSA Guidelines, unless *Pseudomonas* or methicillin-resistant *S. aureus* is suspected (Mandell *et al.*, 2007). Randomized double-blinded studies of adults hospitalized for community-acquired pneumonia have demonstrated that parenteral azithromycin alone was as effective as intravenous cefuroxime, with or without erythromycin (Plouffe *et al.*, 2000; Vergis *et al.*, 2000; Kuzman *et al.*, 2005). Retrospective reviews have also suggested shorter length of stay (Feldman *et al.*, 2003) and lower 30-day mortality (Brown *et al.*, 2003) with azithromycin monotherapy than with those receiving ATS guideline-recommended therapy. However, such patients tended to be younger and were more likely to be in lower-risk groups (Mandell *et al.*, 2007). Azithromycin alone can be considered for hospitalized patients with nonsevere community-acquired pneumonia and no risk factors for infection with drug-resistant *S. pneumoniae* or Gram-negative pathogens (Mandell *et al.*, 2007).

A combination of azithromycin with amoxicillin-clavulanate (see Chapter 14, Amoxicillin-Clavulanic Acid (Co-Amoxiclav)) is recommended in countries with high rates of macrolide-resistant pneumococci when treatment for "atypical" pathogens is suitable (Garcia *et al.*, 2005; Mandell *et al.*, 2007; Tamm *et al.*, 2007).

Among the macrolides, azithromycin (500 mg once daily) is as clinically effective and as well tolerated as a 10-day course of clarithromycin (250 mg twice daily) in mild-moderate community-acquired pneumonia (O'Doherty and Muller, 1998). In hospitalized patients with moderate-to-severe community-acquired pneumonia, the combination of azithromycin and ceftriaxone was equivalent in efficacy and safety to ceftriaxone plus clarithromycin or erythromycin (Tamm *et al.*, 2007).

Azithromycin prophylaxis to asymptomatic employees during a hospital outbreak of *M. pneumoniae*, suggested azithromycin may be of value in reducing clinical illness, although carriage rates are similar (Hyde *et al.*, 2001).

Indications of the extended-release formulation of azithromycin are limited to pneumonia in both children and adults, and to sinusitis

in adults. D'Ignazio *et al.* (2005) demonstrated in a randomized double-blind noninferiority study that single-dose extended-release formulation azithromycin (2 g) was at least as effective as a 7-day course of levofloxacin for the treatment of mild-to-moderate community-acquired pneumonia (D'Ignazio *et al.*, 2005). In a randomized double-blind study, single-dose extended-release azithromycin (2 g) was as effective as a 7-day course of clarithromycin for mild-to-moderate community-acquired pneumonia in adults, with 92.8% pathogen eradication rates and 92.6% cure rates (Drehobl *et al.*, 2005).

7c. Pertussis

Azithromycin is preferred for the treatment of pertussis in persons aged <1 month, and is an alternative to other macrolides in older children and adults, although data on safety and efficacy of azithromycin use among infants aged <6 months are limited (Tiwari *et al.*, 2005). Azithromycin (10 mg/kg/day for 5 days; 500 mg in a single dose on day 1, followed by 250 mg daily on days 2–5) is as effective as erythromycin (40 mg/kg/day in three divided doses for 10 days), is better tolerated, and is associated with fewer and milder side-effects (Langley *et al.*, 2004). For postexposure prophylaxis, the benefits of administering an antimicrobial agent to reduce the risk of pertussis should be weighed against the potential adverse effects of the drug. The Centers for Disease Control (CDC) recommends administration of postexposure prophylaxis of asymptomatic household contacts within 21 days of onset of cough in the index patient (Tiwari *et al.*, 2005). The recommended antimicrobial agents and dosing are the same as those for the treatment of pertussis.

7d. Skin and skin structure infections

Azithromycin is indicated for uncomplicated skin and skin-structure infections due to *S. aureus*, *S. pyogenes*, or *S. agalactiae*. Antibiotics with antiinflammatory properties, such as the tetracyclines and macrolides, are the agents of choice for pustulopustular acne (Zouboulis and Piquero-Martin, 2003). For acne vulgaris, 12 weeks' treatment with azithromycin 500 mg for 4 days per month was efficient with a favorable safety profile in a prospective randomized trial (Parsad *et al.*, 2001). Two open-label noncomparative studies have shown the effectiveness of azithromycin 500 mg three times a week for 8–12 weeks (Kapadia and Talib, 2004; Bardazzi *et al.*, 2007).

7e. Tick-borne infections and other zoonoses

Lyme disease

Azithromycin is an alternative for early localized or disseminated Lyme disease (*Borrelia* spp.) associated with erythema migrans or borrelial lymphocytoma, although it has been found in clinical trials to be less effective than other antimicrobials such as doxycycline, amoxicillin, and cefuroxime (Wormser *et al.*, 2006). The Infectious Diseases Society of America reserves the use of azithromycin (children: 10 mg/kg/day to a maximum of 500 mg; adults: 500 mg daily for 7–10 days) for patients who are intolerant of, or who should not take, amoxicillin, doxycycline, and cefuroxime axetil (Wormser *et al.*, 2006).

Babesiosis

The combination of atovaquone plus azithromycin (children: 10 mg/kg/day for day 1, 5 mg/kg/day after; adults: 500–100 mg on day 1, followed by 250 mg/day after) or clindamycin plus quinine for 7–10 days is recommended by the Infectious Diseases Society of America for the initial therapy of babesiosis (Wormser *et al.*, 2006). Severe babesiosis should be treated with quinine and azithromycin. Higher

doses of azithromycin (600–1000 mg/day) may be used in immunocompromised patients.

Scrub typhus and leptospirosis

Doxycycline is standard therapy for scrub typhus in nonpregnant adults. There have been reports of doxycycline-resistant strains of *Orientia tsutsugamushi* in Northern Thailand (Watt *et al.*, 1996b). The efficacy of azithromycin was recently compared with doxycycline in the treatment of acute fever (<15 days) without an obvious focus, in a randomized controlled trial in Thailand (Phimda *et al.*, 2007). Two hundred and ninety-six patients were randomized to either a 7-day course of doxycycline or a 3-day course of doxycycline. The cause of the fever was determined in 51%; 69 patients (23.3%) had leptospirosis, 57 (19.3%) had scrub typhus, 14 (4.7%) had murine typhus, and 11 (3.7%) had evidence of both leptospirosis and a rickettsial infection. Similar fever clearance times were obtained between the two treatment arms. For leptospirosis, fever clearance within 48 hours was 55.9% for doxycycline compared with 65.7% for azithromycin ($p = 0.33$). For scrub typhus, median time to fever clearance was 48 hours for doxycycline compared with 60 hours for azithromycin ($p = 0.13$). Significantly more patients treated with doxycycline became afebrile within 48 hours. Azithromycin was better tolerated and no relapses occurred in either group during a one-month follow-up period. Although doxycycline is an excellent initial agent for scrub typhus, azithromycin is an alternative, particularly in pregnancy given its favorable pregnancy outcomes (Kim *et al.*, 2006), and may play a role in doxycycline-resistant strains (Kim *et al.*, 2004; Phimda *et al.*, 2007). Similarly, azithromycin is an alternative to doxycycline in pregnant women for the treatment of leptospirosis (Phimda *et al.*, 2007).

7f. Sexually transmitted diseases

Chlamydia trachomatis

The CDC recommends either single-dose azithromycin (1 g) or doxycycline (100 mg twice daily for 7 days) for the treatment of chlamydial genital infections, although single-dose regimens have improved compliance (Workowski and Berman, 2006). In genital chlamydial infections, a meta-analysis of 12 randomized clinical trials found azithromycin (single 1 g dose) and doxycycline 100 mg (twice daily for 7 days) to be equally efficacious in achieving microbial cure (97% and 98%, respectively) and to have similar tolerability (Lau and Qureshi, 2002). Azithromycin is recommended for treatment of pregnant women because of its favorable safety profile compared with other agents such as doxycycline (Workowski and Berman, 2006).

Patients with *C. trachomatis* infections are frequently coinfecting with *N. gonorrhoeae* and should receive a treatment regime effective against both infections (Workowski and Berman, 2006). Owing to the increasing prevalence of fluoroquinolone-resistant *N. gonorrhoeae*, the CDC no longer recommends the use of fluoroquinolones (Centers for Disease Control and Prevention, 2007). Only one class of drugs, the cephalosporins, are recommended for the treatment of gonorrhoea.

Haemophilus ducreyi

Azithromycin is recommended by the CDC as first-line therapy for genital ulcer disease in men due to *H. ducreyi* (chancroid) (Workowski and Berman, 2006). However, the efficacy of azithromycin in the treatment of chancroid in women has not been established because of the low number of women included in clinical trials. Evidence is limited in the treatment of chancroid in HIV-infected patients, who tend to have slow-healing ulcers (Workowski and Berman, 2006). Close follow-up should occur in HIV-infected patients as they may require longer treatment.

Treponema pallidum

Although penicillin is the recommended treatment of early syphilis, preliminary data suggest that single-dose azithromycin (2 g) may be effective (Hook *et al.*, 2002; Riedner *et al.*, 2005). A randomized study in Tanzania of 328 subjects found single-dose oral azithromycin (2 g) to be as effective as penicillin G benzathine in treating early and latent syphilis, with 97.7% and 95% cure rates, respectively, after treatment, and 85.5% and 81.5%, respectively, at six months follow-up. However, several cases of azithromycin failure have been reported and resistance to azithromycin has been documented in several geographic areas, limiting the use of azithromycin to macrolide-susceptible *T. pallidum* areas (Lukehart *et al.*, 2004; Mitchell *et al.*, 2006). The CDC recommends azithromycin for the treatment of early syphilis in patients who are allergic to both penicillin and ceftriaxone (Riedner *et al.*, 2005).

Other sexually transmitted diseases

Azithromycin (1 g once per week for at least 3 weeks and until all lesions have healed) is a second-line treatment for granuloma inguinale (donovanosis) (Workowski and Berman, 2006). *M. genitalium* may respond better to azithromycin than to doxycycline (Falk *et al.*, 2003).

7g. *Mycobacterium avium* complex infection

Pulmonary *Mycobacterium avium* complex disease

Before the introduction of macrolides, antimicrobial therapy of pulmonary MAC disease in HIV-negative patients yielded inconsistent results, largely because of toxicity and poor *in vivo* activity (Griffith *et al.*, 2007). The newer macrolides have been a major therapeutic advance with substantial *in vitro* and clinical activity against MAC, which is attributed to their high concentration in phagocytes and tissues. All untreated strains of MAC are macrolide susceptible and microbiologic and clinical relapses are associated with the development of a point mutation in the macrolide-binding region (peptidyltransferase) of the 23S rRNA gene (Jost *et al.*, 1995; Nash and Indelied, 1995; Springer *et al.*, 1996). This mutation, measured by clarithromycin sensitivity testing (MICs >32 µg/ml), confers cross-resistance between clarithromycin and azithromycin, and presumably all macrolides (Heifets *et al.*, 1993). Macrolides should not be used as single agents, as resistance of *M. avium* develops (Chaisson *et al.*, 1994; Wallace *et al.*, 1994). In a prospective, noncomparative trial, patients with MAC pulmonary disease received azithromycin 600 mg/day as monotherapy for four months (Griffith *et al.*, 1996). Other agents, including streptomycin, ethambutol, and rifabutin or rifampicin, were added after four months, or when the sputum converted to AFB negative. Sputum conversion rates were 67% at six months, which was similar to clarithromycin (74%) in a similar trial (Griffith *et al.*, 2007). Together with the companion drugs, there was no difference in treatment success, defined by 12 months of negative sputum cultures whilst on therapy, between daily administration of azithromycin (300–600 mg) and three times per week (600 mg) administration, with rates of 59% and 55–65%, respectively (Griffith *et al.*, 2001).

Ethambutol (+ rifampicin) is used in first-line combinations with azithromycin (Benison, 1994; Griffith *et al.*, 2007); amikacin, moxifloxacin, or isoniazid are generally considered only in cases of resistance (Griffith *et al.*, 2007). For those patients who do not tolerate a daily treatment, intermittent, three-times-weekly therapy is recommended that includes (1) azithromycin 500–600 mg or clarithromycin 1000 mg, (2) ethambutol 25 mg/kg, and (3) rifampicin 600 mg given three times weekly. The more aggressive (but less well tolerated) treatment regimen for patients with severe and extensive disease consists of azithromycin 250 mg/day or clarithromycin

1000 mg/day (or 500 mg twice daily), rifabutin 150–300 mg/day or rifampicin 10 mg/kg/day (maximum 600 mg/day), ethambutol (15 mg/kg/day), and consideration of inclusion of either amikacin or streptomycin for the first two or three months of therapy (Griffith *et al.*, 2007).

Disseminated *Mycobacterium avium* complex in patients with AIDS

Successful treatment of disseminated MAC in persons with AIDS requires therapy targeting both the mycobacterial infection and the HIV infection to improve the underlying immunosuppression (Griffith *et al.*, 2007). Close monitoring is required for adverse drug effects and drug interactions. Combination therapy is recommended, and both clarithromycin and azithromycin have been shown to be effective, although clarithromycin tends to clear bacteremia more quickly (Gordin *et al.*, 1999; Lam *et al.*, 2006). Recommended initial therapy for disseminated MAC is azithromycin 250 mg/day or clarithromycin 1000 mg/day (or 500 mg twice daily), rifabutin 150–300 mg/day or rifampicin 10 mg/kg/day (maximum 600 mg/day), and ethambutol (15 mg/kg/day) (Griffith *et al.*, 2007). As with pulmonary MAC, amikacin or moxifloxacin are generally considered only in cases of resistance. Treatment of MAC in patients with AIDS should be considered life-long, unless immune restoration is achieved by antiretroviral therapy (Griffith *et al.*, 2007).

Azithromycin is the preferred macrolide for prophylaxis of MAC infections because of its easier therapeutic scheme (1200 mg once weekly), which favors compliance and therefore decreases the risk for selection of resistance (Oldfield *et al.*, 1998).

7h. Gastrointestinal infections

Azithromycin is an alternative for the treatment of traveler's diarrhea, particularly in the setting of high levels of resistance to the more commonly used fluoroquinolones in returned travelers (Cabada and White, 2008; Threlfall *et al.*, 2008). Azithromycin is similar to levofloxacin for the treatment of returned US travelers with acute diarrhea acquired in Mexico and Turkey (Adachi *et al.*, 2003; Sanders *et al.*, 2007). Single-dose (1 g) azithromycin is recommended for empirical therapy of traveler's diarrhea acquired in Thailand (Tribble *et al.*, 2007).

Salmonella typhi and *Salmonella paratyphi*

Numerous trials, which included multiple-drug-resistant (resistant to chloramphenicol, ampicillin, and cotrimoxazole) or nalidixic acid-resistant strains of *S. typhi* or *S. paratyphi* (52–96% of study participants), have demonstrated that azithromycin significantly reduced clinical failure and duration of hospital stay compared with the fluoroquinolones, ofloxacin and gatifloxacin (Chinh *et al.*, 2000; Parry *et al.*, 2007; Dolecek *et al.*, 2008; Effa and Bukirwa, 2008). Compared with ceftriaxone, azithromycin has similar clinical outcomes in the treatment of enteric fever, although azithromycin significantly reduces the rate of relapse (Frenck *et al.*, 2000; Frenck *et al.*, 2004; Effa and Bukirwa, 2008). In the UK, the reference center for *Salmonella enterica* serovars Typhi and Paratyphi A screens isolates from all cases of infection for resistance, and, currently, none of the isolates have exhibited resistance to azithromycin (Threlfall *et al.*, 2008).

Shigellosis

Azithromycin is recommended by the American Academy of Pediatrics for the treatment of shigellosis in children, and by the World Health Organization as a second-line treatment in adults (WHO, 2005; Boumghar-Bourtchai *et al.*, 2008). However, recent data have suggested rapid emergence of resistance in shigella isolates in France

and Bangladesh, which may limit the use of azithromycin in regional areas (Rahman *et al.*, 2007; Boumghar-Bourtchai *et al.*, 2008).

Cholera

Azithromycin is indicated in the treatment of severe cholera in adults and children. Single-dose azithromycin (1 g) was compared with single-dose ciprofloxacin (1 g) in a randomized, double-blind trial in Bangladesh involving 195 men with severe cholera caused by *V. cholerae* (Saha *et al.*, 2006). Bacteriologic success was achieved in 78% of the azithromycin arm, compared with 10% in the ciprofloxacin arm. Shorter duration of diarrhea occurred with azithromycin. The diminished efficacy of ciprofloxacin may result from its diminished activity against *V. cholerae* circulating in Bangladesh.

Helicobacter pylori

The American College of Gastroenterology recommends a proton pump inhibitor, clarithromycin, and amoxicillin for the eradication of *H. pylori* infection (Chey *et al.*, 2007). Azithromycin has been considered as an alternative to clarithromycin owing to its ease of administration; however, low eradication rates have prevented its widespread use (Blandizzi *et al.*, 1998; Sullivan *et al.*, 2002; Silva *et al.*, 2008). Although azithromycin reaches high concentration in plasma and gastric mucosa, the low eradication rates can be explained by its low concentration in the gastric juice (Krichhoff *et al.*, 1999).

7i. Trachoma

Antibiotic therapy is aimed at reducing the burden of infection of trachoma, which in turn reduces progressive trachomatous scarring, although there is currently little direct evidence to support this (Burton, 2007). A single oral dose of azithromycin (20 mg/kg up to a maximum dose of 1 g) is equally effective as topical tetracycline applied twice daily for 6 weeks (Bailey *et al.*, 1993). Mass community-wide treatment with azithromycin in endemic areas has produced a marked reduction in the prevalence of Chlamydial infection (Schachter *et al.*, 1999; Solomon *et al.*, 2004; Burton *et al.*, 2005). There is growing concern that infection may return to communities that have lost some of their immunity to *Chlamydia* after antibiotics are discontinued (Brunham *et al.*, 2005; Atik *et al.*, 2006). Therefore, local elimination is not only preferable, but may be attainable. Solomon *et al.* (2004) reported the effect of high-coverage, single-dose mass azithromycin treatment on ocular *C. trachomatis* infection in a community of 978 people in Tanzania, of whom 97.6% of residents were treated; the prevalence fell from 9.5% at baseline to 0.1% 24 months later (Solomon *et al.*, 2004). A second round of mass treatment occurred at 24 months. Three years after the second mass treatment, *C. trachomatis* DNA was not detected on the conjunctiva of any of the 859 residents tested (Solomon *et al.*, 2008). Melese *et al.* (2008) compared annual and biannual mass antibiotic administration in severely affected villages in Ethiopia. Overall, 14,897 of 16,403 eligible individuals (90.8%) received their scheduled treatment. In the villages treated annually, the prevalence fell from 42% to 6.8% at 24 months, whereas in the villages treated biannually, prevalence fell from 31.6% to 0.9% at 24 months. The World Health Organization currently recommends annual mass azithromycin treatment for three years in communities in which the prevalence of the clinical sign "trachomatous inflammation-follicular" in children between one and nine years of age is 10% or more.

7j. Malaria

The spread of multidrug resistance to *P. falciparum* has led to interest in the development of antimalarial compounds with novel modes of action. In addition, artemisinin-based combination therapies have become standard of care for the treatment of *P. falciparum*. Azithromycin has been evaluated in phase II clinical trials, and further development is underway (Noedl *et al.*, 2006). Compared with

other antibiotics used for malaria (e.g. tetracyclines), azithromycin is favorable because of its safety in children and pregnancy. Azithromycin is relatively slow acting and therefore has to be combined with faster-acting compounds that will quickly reduce parasite burden (Noedl *et al.*, 2007). Azithromycin has intrinsic activity against *Plasmodium* spp. both *in vitro* and *in vivo* for prophylaxis and treatment (Anderson *et al.*, 1998; Ohrt *et al.*, 2002; Dunne *et al.*, 2005; Heppner *et al.*, 2005; Miller *et al.*, 2006; Noedl *et al.*, 2006). Noedl *et al.* (2007) recently confirmed that azithromycin, in combination with artemisinin derivatives or quinine, exerts additive to synergistic interactions, shows no cross-sensitivity with traditional antimalarials and has substantial antimalarial activity on its own (Noedl *et al.*, 2007). Azithromycin in combination with faster-acting antimalarials has demonstrated efficacy in phase II trials in treating *P. falciparum* malaria (Dunne *et al.*, 2005; Miller *et al.*, 2006; Noedl *et al.*, 2006). Although promising, azithromycin is not currently recommended in clinical practice guidelines for the treatment of malaria (WHO, 2006; Gilbert *et al.*, 2008).

7k. Coronary artery disease

An association between *C. pneumoniae* and atherogenesis has been suggested from various epidemiologic, laboratory, animal, and clinical studies. However, causality has not been established. Macrolides have been suggested to play a protective role against coronary artery disease, as a result of an antichlamydial or an anti-inflammatory effect on atheromata. Several large randomized trials examining antimicrobial therapy in stable coronary artery disease, postmyocardial infarction, and acute coronary artery disease have failed to demonstrate any significant reduction in coronary events. The ACES trial, a randomized prospective trial, evaluated 4012 patients with stable coronary artery disease (Grayston *et al.*, 2005). Participants were randomized to placebo or 600 mg azithromycin weekly for one year, and follow-up was for a mean of 3.9 years. The Wizard study randomized 7747 patients with previous myocardial infarction at least 6 weeks previously and a *C. pneumoniae* immunoglobulin G titer of 1:16 or more, to placebo or azithromycin (600 mg/day for 3 days during week 1, then 600 mg/week during weeks 2–12) (O'Connor *et al.*,

2003). Follow-up was a median of 14 months. The AZACS trial assigned 1439 patients with an acute myocardial infarction or unstable angina to a 5-day course of azithromycin (500 mg on the first day, then 250 mg daily) or placebo (Cercek *et al.*, 2003), and followed patients for six months. Other studies, which include other antimicrobials, have also failed to demonstrate significant benefit of antimicrobial therapy (Muhlestein *et al.*, 2000; Leowattana *et al.*, 2001; Sinisalo *et al.*, 2002; Wells *et al.*, 2004; Cannon *et al.*, 2005). A recent meta-analysis did not show any benefit with azithromycin in the secondary prevention of coronary artery disease (Baker and Couch, 2007). In addition, there is some evidence that the use of azithromycin and clarithromycin in coronary heart disease may significantly increase cardiovascular mortality (Jespersen *et al.*, 2006). Currently, insufficient evidence exists for the use of antichlamydial therapy in the secondary prevention of cardiovascular disease (Danesh, 2005; Watson and Alp, 2008).

7l. Use as an immunomodulating agent

Azithromycin is increasingly used as an immunomodulating agent in cystic fibrosis patients, although its mechanism of action remains unclear (Dinwiddie, 2005; Elizur *et al.*, 2008). Interestingly, azithromycin, although not directly active against *P. aeruginosa*, may have indirect actions against this organism. A Cochrane systematic review concluded that there is evidence from studies of a small but significant improvement in respiratory function among cystic fibrosis patients after treatment with azithromycin (Southern *et al.*, 2004). Recent clinical studies show that once-weekly azithromycin ameliorates inflammatory reactions and improved quality of life in cystic fibrosis patients chronically infected with *P. aeruginosa* (Steinkamp *et al.*, 2008), and that oral azithromycin three times weekly for 12 months significantly reduces the number of pulmonary exacerbations, the time elapsed before the first pulmonary exacerbation and the number of additional courses of oral antibiotics, regardless of the infectious status of the patient (Clement *et al.*, 2006). Nevertheless, the role and use of azithromycin for this indication appears to vary between specialist centers currently managing cystic fibrosis patients.

References

- Adachi JA, Ericsson CD, Jiang ZD *et al.* (2003). Azithromycin found to be comparable to levofloxacin for the treatment of US travellers with acute diarrhea acquired in Mexico. *Clin Infect Dis* 37: 1165–71.
- Aldridge KE, Cammarata C, Martin DH (1993). Comparison of the *in vitro* activities of various parenteral and oral antimicrobial agents against endemic *Haemophilus ducreyi*. *Antimicrob Agents Chemother* 37: 1986–8.
- American Thoracic Society/European Respiratory Society Task Force (2004). Standards for the Diagnosis and Management of Patients with COPD. Version 1.2. New York: American Thoracic Society. Available from: www.thoracic.org/go/copd. Accessed December 2009.
- Amsden GW, Nafziger AN, Foulds G, Cabelus LJ (2000). A study of the pharmacokinetics of azithromycin and nelfinavir when coadministered in healthy volunteers. *J Clin Pharmacol* 40: 1522–7.
- Amsden GW, Baird IM, Simon S, Treadway G (2003). Efficacy and safety of azithromycin vs levofloxacin in the outpatient treatment of acute bacterial exacerbations of chronic bronchitis. *Chest* 123: 772–7.
- Andes D, Anon J, Jacobs MR, Craig WA (2004). Application of pharmacokinetics and pharmacodynamics to antimicrobial therapy of respiratory tract infections. *Clin Lab Med* 24: 477–502.
- Anderson SL, Oloo AJ, Gordon DM *et al.* (1998). Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in Western Kenya. *Clin Inf Dis* 26: 146–50.
- Anthonisen NR, Manfreda J, Warren CP *et al.* (1987). Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 106: 196–204.
- Apseloff G, Foulds G, LaBoy-Goral L *et al.* (1998). Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *J Clin Pharmacol* 38: 830–5.
- Araujo FG, Guptill DR, Remington JS (1988). Azithromycin, a macrolide antibiotic with potent activity against *Toxoplasma gondii*. *Antimicrob Agents Chemother* 32: 755–7.
- Arguedas A, Loaiza C, Herrera ML, Mohs E (1996). Comparative trial of three days of azithromycin versus ten days of amoxicillin clavulanate potassium in the treatment of children with acute otitis media with effusion. *Int J Antimicrob Agents* 6: 233–8.
- Arguedas A, Loaiza C, Herrera ML, Mohs E (1997). Comparative trial of three days of azithromycin versus ten days of clarithromycin in the treatment of children with acute otitis media with effusion. *J Chemother* 9: 44–50.
- Arguedas A, Loaiza C, Perez A *et al.* (2003). A pilot study of single-dose azithromycin versus 3-day azithromycin or single-dose ceftriaxone for uncomplicated acute otitis media in children. *Curr Ther Res* 64 (Suppl A): A16–29.
- Arguedas A, Emparanz P, Schwartz RH *et al.* (2005). A randomized, multicenter, double blind, double dummy trial of single dose azithromycin

- versus high dose amoxicillin for treatment of uncomplicated acute otitis media. *Pediatr Infect Dis J* 24: 153–61.
- Aronoff GR, Berns JS, Brier ME *et al.* (1999). *Drug prescribing in renal failure: Dosing guidelines for adults*, 4th edn. Philadelphia: American College of Physicians.
- Atik B, Thanh TT, Luong VQ *et al.* (2006). Impact of annual targeted treatment on infectious trachoma and susceptibility to reinfection. *JAMA* 296: 1488–97.
- Aubry A, Jarlier V, Escolano S *et al.* (2000). Antibiotic susceptibility pattern of *Mycobacterium marinum*. *Antimicrob Agents Chemother* 44: 3133–6.
- Bach PB, Brown C, Gelfand SE, McCrory DC (2001). Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. *Ann Intern Med* 134: 600–20.
- Bachmann K, Jauregui L, Chandra R, Thaker K (2003). Influence of a 3-day regimen of azithromycin on the disposition kinetics of cyclosporine A in stable renal transplant patients. *Pharmacol Res* 47: 549–54.
- Bailey RL, Arullendran P, Whittle HC, Mabey DC (1993). Randomised controlled trial of single-dose azithromycin in treatment of trachoma. *Lancet* 342: 453–6.
- Baker WL, Couch KA (2007). Azithromycin for the secondary prevention of coronary artery disease: a meta-analysis. *Am J Health Syst Pharm* 64: 830–6.
- Ballow CH, Amsden GW, Highet VS, Forrest A (1998). Pharmacokinetics of oral azithromycin in serum, urine, polymorphonuclear leucocytes and inflammatory vs non-inflammatory skin blisters in healthy volunteers. *Clin Drug Investig* 15: 159–67.
- Bar-Oz B, Diav-Citrin O, Shechtman S *et al.* (2008). Pregnancy outcome after gestational exposure to the new macrolides: a prospective multicenter observational study. *Eur J Obstet Gynecol Reprod Biol* 141: 31–4.
- Barcia-Macay M, Seral C, Mingeot-Leclercq MP *et al.* (2006). Pharmacodynamic evaluation of the intracellular activities of antibiotics against *Staphylococcus aureus* in a model of THP-1 macrophages. *Antimicrob Agents Chemother* 50: 841–51.
- Bardazzi F, Savoia F, Parente G *et al.* (2007). Azithromycin: a new therapeutical strategy for acne in adolescents. *Dermatol Online J* 13: 4.
- Barry AL, Fuchs PC (1995). *In vitro* activities of a streptogramin (RP59500), three macrolides, and an azalide against four respiratory tract pathogens. *Antimicrob Agents Chemother* 39: 238–40.
- Barry AL, Jones RN, Thornberry C (1988). *In vitro* activities of azithromycin (CP 62,993), clarithromycin (A-56268; TE-031), erythromycin, roxithromycin, and clindamycin. *Antimicrob Agents Chemother* 32: 752–4.
- Beckey NP, Parra D, Colon A (2000). Retrospective evaluation of a potential interaction between azithromycin and warfarin in patients stabilized on warfarin. *Pharmacotherapy* 20: 1055–9.
- Benson CA (1994). Treatment of disseminated disease due to the *Mycobacterium avium* complex in patients with AIDS. *Clin Infect Dis* 18 (Suppl 3): S237–42.
- Bermudez LE, Young LS (1988). Activities of amikacin, roxithromycin, and azithromycin alone or in combination with tumor necrosis factor against *Mycobacterium avium* complex. *Antimicrob Agents Chemother* 32: 1149–53.
- Bermudez LE, Inderlied C, Young LS (1991). Stimulation with cytokines enhances penetration of azithromycin into human macrophages. *Antimicrob Agents Chemother* 35: 2625–9.
- Bizjak ED, Haug 3rd MT, Schilz RJ *et al.* (1999). Intravenous azithromycin-induced ototoxicity. *Pharmacotherapy* 19: 245–8.
- Blais J, Beauchamp D, Chamberland S (1994). Azithromycin uptake and intracellular accumulation by *Toxoplasma gondii*-infected macrophages. *J Antimicrob Chemother* 34: 371–82.
- Blandizzi C, Malizia T, Gherardi G *et al.* (1998). Gastric mucosal distribution and clinical efficacy of azithromycin in patients with *Helicobacter pylori* related gastritis. *Antimicrob Chemother* 42: 75–82.
- Block SL, Arrieta A, Seibel M *et al.* (2003). Single dose (30 mg/kg) azithromycin compared with 10-day amoxicillin/clavulanate for the treatment of uncomplicated acute otitis media. *Curr Ther Res* 64 (Suppl A): A30–42.
- Boumghar-Bourtchai L, Mariani-Kurkdjian P, Bingen E *et al.* (2008). Macrolide-resistant *Shigella sonnei*. *Emerg Infect Dis* 14: 1297–9.
- Bradbury F (1993). Comparison of azithromycin versus clarithromycin in the treatment of patients with lower respiratory tract infection. *J Antimicrob Chemother* 31 (Suppl): 153–62.
- Bright GM, Nagel AA, Bordner J *et al.* (1988). Synthesis, *in vitro* and *in vivo* activity of novel 9-deoxo-9a-AZA-9a-homoerythromycin A derivatives; a new class of macrolide antibiotics, the azalides. *J Antibiot (Tokyo)* 41: 1029–47.
- Brook I, Hausfeld JN (2006). Effect of telithromycin and azithromycin on nasopharyngeal bacterial flora in patients with acute maxillary sinusitis. *Arch Otolaryngol Head Neck Surg* 132: 442–5.
- Brown BA, Griffith DE, Giard W *et al.* (1997). Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin Infect Dis* 24: 958–64.
- Brown RB, Iannini P, Gross P, Kunkel M (2003). Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest* 123: 1503–11.
- Brunham RC, Pourbahloul B, Mak S *et al.* (2005). The unexpected impact of a *Chlamydia trachomatis* infection control program on susceptibility to reinfection. *J Infect Dis* 192: 1836–44.
- Brunton S, Iannini P (2005). Macrolide-resistant *Streptococcus pneumoniae*: clinical implications for the empiric treatment of community-acquired respiratory tract infections. *MedGenMed* 7: 63.
- Burton MJ (2007). Trachoma: An overview. *Br Med Bull* 84: 99–116.
- Burton MJ, Holland MJ, Makalo P *et al.* (2005). Re-emergence of *Chlamydia trachomatis* infection after mass antibiotic treatment of a trachoma-endemic Gambian community: a longitudinal study. *Lancet* 365: 1321–8.
- Cabada MM, White Jr AC (2008). Travellers' diarrhea: An update on susceptibility, prevention and treatment. *Curr Gastroenterol Rep* 10: 473–9.
- Cadisch R, Streit E, Hartmann K (1996). [Exacerbation of pseudoparalytic myasthenia gravis following azithromycin (Zithromax)]. *Schweiz Med Wochenschr* 126: 308–10.
- Cannon CP, Braunwald E, McCade CH *et al.* (2005). Antibiotic treatment of *Chlamydia pneumoniae* after acute coronary syndrome. *N Engl J Med* 352: 1646–54.
- Canton R, Loza E, Morosini MI, Baquero F (2002). Antimicrobial resistance amongst isolates of *Streptococcus pyogenes* and *Staphylococcus aureus* in the PROTEKT antimicrobial surveillance programme during 1999–2000. *J Antimicrob Chemother* 50 (Suppl S1): 9–24.
- Carceles CM, Fernandez-Varon E, Marin P, Escudero E (2007). Tissue disposition of azithromycin after intravenous and intramuscular administration to rabbits. *Vet J* 174: 154–9.
- Carlier MB, Garcia-Luque I, Montenez JP *et al.* (1994). Accumulation, release and subcellular localization of azithromycin in phagocytic and non-phagocytic cells in culture. *Int J Tissue React* 16: 211–20.
- Cascaval RI, Lancaster DJ (2001). Hypersensitivity syndrome associated with azithromycin. *Am J Med* 25: 483–4.
- Catnach SM, Fairclough PD (1992). Erythromycin and the gut. *Gut* 33: 397–401.
- Centers for Disease Control and Prevention (CDC) (2007). Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for the treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep* 56: 332–6.
- Cercek B, Shah PK, Noc M *et al.* (2003). Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomized controlled trial. *Lancet* 361: 809–13.
- Chaisson RE, Benson CA, Dube MP *et al.* (1994). Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. *Ann Intern Med* 121: 905–11.
- Chandra R, Liu P, Breen JD *et al.* (2007). Clinical pharmacokinetics and gastrointestinal tolerability of a novel extended-release microsphere formulation of azithromycin. *Clin Pharmacokinet* 46: 247–59.
- Chandrupatla S, Demetris AJ, Rabinovitz M (2002). Azithromycin-induced intrahepatic cholestasis. *Dig Dis Sci* 47: 2186–8.
- Chave JB, Munafo A, Chatton JY *et al.* (1992). Once-a-week azithromycin in AIDS patients: tolerability, kinetics, and effects on zidovudine disposition. *Antimicrob Agents Chemother* 32: 1013–18.

- Chen SC, Gottlieb T, Palmer JM *et al.* (1992). Antimicrobial susceptibility of anaerobic bacteria in Australia. *J Antimicrob Chemother* 30: 811–20.
- Chey WD, Wong BC, Practice Parameters Committee of the American College of Gastroenterology (2007). American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 102: 1808–25.
- Chiambaretta F, Garraffo R, Elena PP *et al.* (2008). Tear concentrations of azithromycin following topical administration of a single dose of azithromycin 0.5%, 1.0%, and 1.5% eyedrops (T1225) in healthy volunteers. *Eur J Ophthalmol* 18: 13–20.
- Chinh NT, Parry CM, Ly NT *et al.* (2000). A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. *Antimicrob Agents Chemother* 44: 1855–9.
- Clement A, Tamalet A, Leroux E *et al.* (2006). Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax* 61: 895–902.
- Cooper MA, Nye K, Andrews JM, Wise R (1990). The pharmacokinetics and inflammatory fluid penetration of orally administered azithromycin. *J Antimicrob Chemother* 26: 533–8.
- Contopoulos-Ionnis DG, Ioannidis JP, Chew P, Lau J (2001). Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for lower respiratory tract infections. *J Antimicrob Chemother* 48: 691–703.
- Crokaert F, Hubloux A, Cauchie P (1998). A Phase I determination of azithromycin in plasma during a 6-week period in normal volunteers after a standard dose of 500 mg once daily for 3 days. *Clin Drug Invest* 16: 161–6.
- Curtis LH, Ostbye T, Sendersky V *et al.* (2003). Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *Am J Med* 114: 135–41.
- Danesh J (2005). Antibiotics in the prevention of heart attacks. *Lancet* 365: 365–7.
- Danesi R, Lupetti A, Barbara C *et al.* (2003). Comparative distribution of azithromycin in lung tissue of patients given oral daily doses of 500 and 1000 mg. *J Antimicrob Chemother* 51: 939–45.
- Davies BI, Maesen FP, Gubbelsmans R (1989). Azithromycin (CP-62,993) in acute exacerbations of chronic bronchitis: an open clinical, microbiological and pharmacokinetic study. *J Antimicrob Chemother* 23: 743–51.
- Davila D, Kolacny-Babic L, Plavsic F (1991). Pharmacokinetics of azithromycin after single oral dosing of experimental animals. *Biopharm Drug Dispos* 12: 505–14.
- de Duye C, de Barys T, Poole B *et al.* (1974). Commentary. Lysosomotropic agents. *Biochem Pharmacol* 23: 2495–531.
- Deabate CA, Mathew CP, Warner JH *et al.* (2000). The safety and efficacy of short course (5-day) moxifloxacin versus azithromycin in the treatment of patients with acute exacerbations of chronic bronchitis. *Respir Med* 94: 1029–37.
- D'Ignazio J, Camere MA, Lewis DE *et al.* (2005). Novel, single-dose microsphere formulation of azithromycin versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired pneumonia in adults. *Antimicrob Agents Chemother* 49: 4035–41.
- Dinwiddie R (2005). Anti-inflammatory therapy in cystic fibrosis. *J Cyst Fibros* 4 (Suppl 2): 45–8.
- Djokic S, Kobrehel G, Lazarevski G (1987). Erythromycin series. XII. Antibacterial *in vitro* evaluation of 10-dihydro-10-deoxo-11-azaerythromycin A: synthesis and structure-activity relationship of its acyl derivatives. *J Antibiot (Tokyo)* 40: 1006–15.
- Dolecek C, Tran TP, Nguyen NR *et al.* (2008). A multi-center randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. *PLoS ONE* 3: e2188.
- Donowitz GR, Earnhardt KI (1993). Azithromycin inhibition of intracellular *Legionella micdadei*. *Antimicrob Agents Chemother* 37: 2261–4.
- Dorani H, Schutzer KM, Sarich TC *et al.* (2007). Pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor ximelagatran co-administered with different classes of antibiotics in healthy volunteers. *Eur J Pharmacol* 63: 571–81.
- Drehobl MA, De Salvo MC, Lewis DE, Breen JD (2005). Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. *Chest* 128: 2230–7.
- Dunbar LM, Farrell DJ (2007). Activity of telithromycin and comparators against isolates of *Legionella pneumophila* collected from patients with community-acquired respiratory tract infections: PROTEKT Years 1–5. *Clin Microbiol Infect* 13: 743–6.
- Dunkin KT, Jones S, Howard AJ (1988). The *in-vitro* activity of CP-62,993 against *Haemophilus influenzae*, *Branhamella catarrhalis*, staphylococci and streptococci. *J Antimicrob Chemother* 21: 405–11.
- Dunne MW, Khurana C, Mohs AA *et al.* (2003). Efficacy of single-dose azithromycin in treatment of acute otitis media in children after a baseline tympanocentesis. *Antimicrob Agents Chemother* 47: 2663–5.
- Dunne MW, Singh N, Shukla M *et al.* (2005). A multicenter study of azithromycin, alone and in combination with chloroquine, for the treatment of acute uncomplicated *Plasmodium vivax* malaria in India. *J Infect Dis* 191: 1582–8.
- Eberl S, Renner B, Neubert A *et al.* (2007). Role of p-glycoprotein inhibition for drug interactions: evidence from *in vitro* and pharmacoepidemiological studies. *Clin Pharmacokinet* 46: 1039–9.
- Edelstein PH, Edelstein MA (1991). *In vitro* activity of azithromycin against clinical isolates of *Legionella* species. *Antimicrob Agents Chemother* 35: 180–1.
- Effa EE, Bukirwa H (2008). Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). *Cochrane Database Syst Rev* 8: CD006083.
- Ehnhage A, Rautiainen M, Fang AF, Sanchez SP (2008). Pharmacokinetics of azithromycin in serum and sinus fluid after administration of extended-release and immediate-release formulations in patients with acute bacterial sinusitis. *Int J Antimicrob Agents* 31: 561–6.
- Elizur A, Cannon CL, Ferkol TW (2008). Airway inflammation in cystic fibrosis. *Chest* 133: 489–95.
- Engler KH, Warner M, George RC (2001). *In vitro* activity of ketolides HMR 3004 and HMR 3647 and seven other antimicrobial agents against *Corynebacterium diphtheriae*. *J Antimicrob Chemother* 47: 27–41.
- Esposito S, Bosis S, Begliatti E *et al.* (2006). Acute tonsillitis associated with atypical bacterial infection in children: natural history and impact of macrolide therapy. *Clin Infect Dis* 43: 206–9.
- Falk L, Frelund H, Jensen JS (2003). Tetracycline treatment does not eradicate *Mycoplasma genitalium*. *Sex Transm Infect* 79: 318–19.
- Farmer S, Li ZS, Hancock RE (1992). Influence of outer membrane mutations on susceptibility of *Escherichia coli* to the dibasic macrolide azithromycin. *J Antimicrob Chemother* 29: 27–33.
- Fattorini L, Baldassarri L, Li YJ *et al.* (2000). Virulence and drug susceptibility of *Mycobacterium celatum*. *Microbiology* 146: 2733–42.
- Feldman RB, Rhew DC, Wong JY *et al.* (2003). Azithromycin monotherapy for patients hospitalized with community-acquired pneumonia: a 31/2-year experience from a veterans affairs hospital. *Arch Intern Med* 163: 1718–26.
- Foster DR, Milan NL (1999). Potential interaction between azithromycin and warfarin. *Pharmacotherapy* 9: 902–08.
- Foulds G, Johnson RB (1993). Selection of dose regimens of azithromycin. *J Antimicrob Chemother* 31 (Suppl E): 39–50.
- Foulds G, Shepard RM, Johnson RB (1990). The pharmacokinetics of azithromycin in human serum and tissues. *J Antimicrob Chemother* 25 (Suppl A): 73–82.
- Foulds G, Hilligoss DM, Henry EB, Gerber N (1991). The effects of an antacid or cimetidine on the serum concentrations of azithromycin. *J Clin Pharmacol* 31: 164–7.
- Foulds G, La Boy-Goral L, Wei GC, Apseloff G (1999). The effect of azithromycin on the pharmacokinetics of indinavir. *J Clin Pharm* 39: 842–6.
- Frencik Jr RW, Nakhla I, Sultan Y *et al.* (2000). Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clin Infect Dis* 31: 1134–8.
- Frencik Jr RW, Mansour A, Nakhla I *et al.* (2004). Short-course azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents. *Clin Infect Dis* 38: 951–7.
- Garcia VE, Mensa J, Martinez JA *et al.* (2005). Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a

- beta-lactam agent versus a beta-lactam agent alone. *Eur J Clin Microbiol Infect Dis* 24: 190–5.
- Garcia-Cobos S, Campos J, Cercenado E *et al.* (2008). Antibiotic resistance in *Haemophilus influenzae* decreased, except for beta-lactamase-negative amoxicillin-resistant isolates, in parallel with community antibiotic consumption in Spain from 1997 to 2007. *Antimicrob Agents Chemother* 52: 2760–6.
- Garcia-Rodriguez JA, Munoz Bellido JL, Fresnadillo MJ, Trujillano I (1993). *In vitro* activities of new macrolides and rifampentine against *Brucella* spp. *Antimicrob Agents Chemother* 37: 911–13.
- Garey KW, Peloquin CA, Godo PG *et al.* (1999). Lack of effect of zafirlukast on the pharmacokinetics of azithromycin, clarithromycin, and 14-hydroxylclarithromycin in healthy volunteers. *Antimicrob Agents Chemother* 43: 1152–5.
- Giacometti A, Burzacchini F, Cirioni O *et al.* (1999). Efficacy of treatment with paromomycin, azithromycin, and nitazoxanide in a patient with disseminated cryptosporidiosis. *Eur J Clin Microbiol Infect Dis* 18: 885–9.
- Giacometti A, Cirioni O, Barchiesi F, Scalise G (2000). Anticryptosporidial activity of ranalexin, lasalocid and azithromycin alone and in combination in cell lines. *J Antimicrob Chemother* 45: 375–7.
- Gilbert DN, Moellering RC, Eliopoulos GM, Sande ME (2008). *The Sanford guide to antimicrobial therapy* 2008, 38th edn. Sperryville, USA: Antimicrobial Therapy, Inc.
- Gingras BA, Jensen JB (1992). Activity of azithromycin (CP-62,993) and erythromycin against chloroquine-susceptible and chloroquine-resistant strains of *Plasmodium falciparum* *in vitro*. *Am J Trop Med Hyg* 47: 378–82.
- Girard AE, Girard D, English AR *et al.* (1987). Pharmacokinetic and *in vivo* studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. *Antimicrob Agents Chemother* 31: 1948–54.
- Girard D, Finegan SM, Dunne MW, Lame ME (2005). Enhanced efficacy of single-dose versus multi-dose azithromycin regimens in preclinical infection models. *J Antimicrob Chemother* 56 (2): 365–71.
- Girgis NI, Butler T, Frenck RW *et al.* (1999). Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. *Antimicrob Agents Chemother* 43: 1441–4.
- Gomez E, Sanchez JE, Aguado S, Alvarez GJ (1996). Interaction between azithromycin and cyclosporin? *Nephron* 73: 724.
- Gordillo ME, Singh KV, Murray BE (1993). *In vitro* activity of azithromycin against bacterial enteric pathogens. *Antimicrob Agents Chemother* 37: 1203–05.
- Gordin FM, Sulam PM, Shafran SD *et al.* (1999). A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex. *Clin Infect Dis* 28: 1080–5.
- Granowitz EV, Tabor KJ, Kirchoffer JB (2000). Potentially fatal interaction between azithromycin and disopyramide. *Pacing Clin Electrophysiol* 23: 1435.
- Grayston JT, Kronmal RA, Jackson LA *et al.* (2005). Azithromycin for the secondary prevention of coronary events. *N Engl J Med* 352: 1637–45.
- Griffith DE, Brown DA, Girard MW *et al.* (1996). Azithromycin activity against *Mycobacterium avium* complex lung disease in patients who were not infected with human immunodeficiency virus. *Clin Infect Dis* 23: 983–9.
- Griffith DE, Brown DA, Girard MW *et al.* (2001). Azithromycin-containing regimens for treatment of *Mycobacterium avium* complex lung disease. *Clin Infect Dis* 32: 1547–3.
- Griffith DE, Aksamit T, Brown-Elliott BA *et al.* (2007). An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 175: 367–416.
- Grunden JW, Fisher KA (1997). Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother* 31: 859–63.
- Gupta S, Banfield C, Kantesaria B *et al.* (2001). Pharmacokinetic and safety profile of desloratadine and fexofenadine when coadministered with azithromycin: a randomized, placebo-controlled, parallel-group study. *Clin Ther* 23: 451–66.
- Hamill J (1993). Multicentre evaluation of azithromycin and penicillin V in the treatment of acute streptococcal pharyngitis and tonsillitis in children. *J Antimicrob Chemother* 31 (Suppl E): 89–94.
- Hammerschlag MR, Qumei KK, Roblin PM (1992). *In vitro* activities of azithromycin, clarithromycin, L-ofloxacin, and other antibiotics against *Chlamydia pneumoniae*. *Antimicrob Agents Chemother* 36: 1573–4.
- Heifets L, Mar N, Vanderkol KJ (1993). *Mycobacterium avium* strains resistant to clarithromycin and azithromycin. *Antimicrob Agents Chemother* 37: 2364–70.
- Heikkinen T, Laine K, Neuvonen PJ, Ekblad U (2000). The transplacental transfer of the macrolide antibiotics erythromycin, roxithromycin and azithromycin. *BJOG* 107: 770–5.
- Henry DC, Riffer E, Sokol WN *et al.* (2003). Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regime for treatment of acute bacterial sinusitis.
- Hoffler D, Koeppe R, Paeske B (1995). Pharmacokinetics of azithromycin in normal and impaired renal function. *Infection* 23: 356–61.
- Heppner DG, Walsh DS, Uthaimongkol N *et al.* (2005). Randomized, controlled double-blind trial of daily oral azithromycin in adults for the prophylaxis of *Plasmodium vivax* malaria in western Thailand. *Am J Trop Med Hyg* 73: 842–9.
- Hook III EW, Martin DH, Stephens J *et al.* (2002). A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for the treatment of early syphilis. *Sex Transm Dis* 29: 486–90.
- Hopkins S (1996). Clinical toleration and safety of azithromycin. *Am J Med* 91 (Suppl. 3A): 40S–5S.
- Horowitz HW, Hsieh TC, Aguero-Rosenfield ME *et al.* (2001). Antimicrobial susceptibility of *Ehrlichia phagocytophila*. *Antimicrob Agents Chemother* 45: 786–8.
- Huang BH, Wu CH, Hsia CP, Yin CC (2007). Azithromycin-induced torsade de pointes. *Pacing Clin Electrophysiol* 30: 1579–82.
- Hubner C, Dietz A, Stremmel W *et al.* (1997). Macrolide-induced Churg–Strauss syndrome in a patient with atopy. *Lancet* 350: 563.
- Hunfield K, Wichelhaus TA, Rodel R *et al.* (2004). Comparison of *in vitro* activities of ketolides, macrolides, and a azalide against the spirochete *Borrelia burgdorferi*. *Antimicrob Agents Chemother* 48: 344–7.
- Hyde TB, Gilbert M, Schwartz SB *et al.* (2001). Azithromycin prophylaxis during a hospital outbreak of *Mycoplasma pneumoniae* pneumonia. *J Infect Dis* 183: 907–12.
- Ioannidis JP, Contopoulos-Ionnis DG, Chew R, Lau J (2001). Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. *J Antimicrob Chemother* 48: 677–89.
- Ishida K, Kaku M, Irfune K *et al.* (1994). *In vitro* and *in vivo* activities of macrolides against *Mycoplasma pneumoniae*. *Antimicrob Agents Chemother* 38: 790–8.
- Ito K, Ogihara K, Kanamitsu S, Itoh T (2003). Prediction of the *in vivo* interaction between midazolam and macrolides based on *in vitro* studies using human liver microsomes. *Drug Metab Dispos* 31: 945–54.
- Jensen JS, Bradshaw CS, Tabrizi SN *et al.* (2008). Azithromycin treatment failure in *Mycoplasma genitalium*-positive patients with nongonococcal urethritis is associated with induced macrolide resistance. *Clin Infect Dis* 47: 1546–53.
- Jespersen CM, Als-Nielsen B, Damgaard M *et al.* (2006). Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. *BMJ* 332: 22–7.
- Johnson RC, Kodner C, Russell M, Girard D (1990). *In vitro* and *in vivo* susceptibility of *Borrelia burgdorferi* to azithromycin. *J Antimicrob Chemother* 25 (Suppl A): 33–8.
- Jonas D, Engels I, Daschner FD, Frank U (2000). The effect of azithromycin on intracellular *Legionella pneumophila* in the Mono Mac 6 cell line at serum concentrations attainable *in vivo*. *J Antimicrob Chemother* 46: 385–90.
- Jones K, Felmingham D, Ridgway G (1988). *In vitro* activity of azithromycin (CP-62,993), a novel macrolide, against enteric pathogens. *Drugs Exp Clin Res* 14: 613–15.
- Just KC, Dunbar DF, Barth SS *et al.* (1995). Identification of *Mycobacterium tuberculosis* and *Mycobacterium avium* complex directly from smear-positive sputum specimens and BACTEC 12B cultures by high performance liquid

- chromatography with fluorescence detection and computer-driven pattern recognition models. *J Clin Microbiol* 33: 1270–7.
- Kapadia N, Talib A (2004). Acne treated successfully with azithromycin. *Int J Dermatol* 43: 766–77.
- Karabulut AK, Uysal II, Acar H, Fazliogullari Z (2008). Investigation of developmental toxicity and teratogenicity of macrolide antibiotics in cultured rat embryos. *Anat Histol Embryol* 37: 369–75.
- Karaunakaran R, Puthuchery SD (2007). *Burkholderia pseudomallei*: in vitro susceptibility to some new and old antimicrobials. *Scand J Infect Dis* 39: 858–61.
- Kezerashvili A, Khattak H, Barsky A *et al.* (2007). Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors. *J Interv Card Electrophysiol* 18: 243–6.
- Khaki P, Bhalla P, Sharma A, Kumar V (2007). Correlation between *in vitro* susceptibility and treatment outcome with azithromycin in gonorrhoea: a prospective study. *Indian J Med Microbiol* 25: 354–7.
- Khurana CM (1996). A multicenter, randomized, open label comparison of azithromycin and amoxicillin/clavulanate in acute otitis media among children attending day care or school. *Pediatr Infect Dis J* 15 (9 Suppl): S24–9.
- Kim YS, Yun HJ, Shim SK *et al.* (2004). A comparative trial of a single dose of azithromycin versus doxycycline for the treatment of mild scrub typhus. *Clin Infect Dis* 39: 1329–35.
- Kim YS, Lee HJ, Chang MY *et al.* (2006). Scrub typhus during pregnancy and its treatment: a case series and review of the literature. *Am J Trop Med Hyg* 75: 955–9.
- Kitzis MD, Goldstein FW, Miegi M, Acar JF (1990). *In-vitro* activity of azithromycin against various Gram-negative bacilli and anaerobic bacteria. *J Antimicrob Chemother* 25 (Suppl A): 15–18.
- Klein JO (1994). Current issues in upper respiratory tract infections in infants and children: rationale for antibacterial therapy. *Pediatr Infect Dis J* 13: S5–9.
- Klemens SP, Cynamon MH (1994). Activities of azithromycin and clarithromycin against nontuberculous mycobacteria in beige mice. *Antimicrob Agents Chemother* 38: 1455–9.
- Kosowska K, Hoellman DB, Lin G *et al.* (2005). Antipneumococcal activity of ceftobiprole, a novel broad-spectrum cephalosporin. *Antimicrob Agents Chemother* 49: 1932–42.
- Krichhoff R, Laufen H, Schacke G *et al.* (1999). Determination of azithromycin in gastric biopsy samples. *Int J Clin Pharmacol Ther* 37: 361–4.
- Kuriyama T, Williams DW, Yanagisawa M *et al.* (2007). Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics. *Oral Microbiol Immunol* 22: 285.
- Kuzman I, Dakovic-Rode O, Oremus M, Banaszak AM (2005). Clinical efficacy and safety of a short regimen of azithromycin sequential therapy vs standard cefuroxime sequential therapy in the treatment of community-acquired pneumonia: an international, randomized, open-label study. *J Chemother* 17: 636–42.
- Landinez R, Linares J, Loza E *et al.* (1992). *In vitro* activity of azithromycin and tetracycline against 358 clinical isolates of *Brucella melitensis*. *Eur J Clin Microbiol Infect Dis* 11: 265–7.
- Lane G (1996). Increased hypoprothrombinemic effect of warfarin possibly induced by azithromycin. *Ann Pharmacother* 30: 1885–6.
- Langley JM, Halperin SA, Boucher FD *et al.* (2004). Azithromycin is as effective as and better tolerated than erythromycin estolate for the treatment of pertussis. *Pediatrics* 114: e96–101.
- Lam PK, Griffith DE, Aksamit TR *et al.* (2006). Factors related to response to intermittent treatment of *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 173: 1283–9.
- Lau CY, Qureshi AK (2002). Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis* 29: 497–502.
- Leclercq R, Courvalin P (1991). Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. *Antimicrob Agents Chemother* 35: 1267–72.
- Leowattana W, Bhuripanyo K, Singhaviranon L *et al.* (2001). Roxithromycin in prevention of acute coronary syndrome associated with *Chlamydia pneumoniae* infection: a randomized placebo controlled trial. *J Med Assoc Thai* 84 (Suppl 3): S669–75.
- Lever MS, Bewley KR, Dowsett B, Lloyd G (2004). *In vitro* susceptibility of *Coxiella burnetii* to azithromycin, doxycycline, ciprofloxacin and a range of newer fluoroquinolones. *J Antimicrob Agents* 24: 194–5.
- Lion C, Conroy MC, Carpentier AM, Lozniewski A (2006). Antimicrobial susceptibilities of *Pasteurella* strains isolated from humans. *Int J Antimicrob Agents* 27: 290–3.
- Ljubic D, Rumboldt Z (1995). Possible interaction between azithromycin and cyclosporine: a case report. *Nephron* 70: 130.
- Lode HM (2007). Managing community-acquired pneumonia: a European perspective. *Respir Med* 101: 1864–73.
- Longo G, Valenti C, Gandini G *et al.* (1997). Azithromycin-induced intrahepatic cholestasis. *Am J Med* 102: 217–18.
- Lucchi M, Damle B, Fang A *et al.* (2008). Pharmacokinetics of azithromycin in serum, bronchial washings, alveolar macrophages and lung tissue following a single oral dose of extended or immediate release formulations of azithromycin. *J Antimicrob Chemother* 61: 884–91.
- Luke DR, Foulds G (1997). Tolerant of intravenous azithromycin. *Ann Pharmacother* 31: 965–9.
- Lukehart SA, Fohn MJ, Baker-Zander SA (1990). Efficacy of azithromycin for therapy of active syphilis in the rabbit model. *J Antimicrob Chemother* 25 (Suppl A): 91–9.
- Lukehart SA, Godornes C, Molini BJ *et al.* (2004). Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Eng J Med* 351: 154–8.
- Mandell LA, Wunderink RG, Anzueto A *et al.* (2007). Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 44 (Suppl 2): S27–72.
- Mansoor GA, Panner BJ, Ornt DB (1993). Azithromycin-induced acute interstitial nephritis. *Ann Intern Med* 119: 636–7.
- Martin IM, Hoffmann S, Ison CA. ESSTI Network (2006). European Surveillance of Sexually Transmitted Infections (ESSTI): the first combined antimicrobial susceptibility data for *Neisseria gonorrhoeae* in Western Europe. *J Antimicrob Chemother* 58: 587–93.
- Maskell JP, Sefton AM, Williams JD (1990). Comparative *in-vitro* activity of azithromycin and erythromycin against Gram-positive cocci, *Haemophilus influenzae* and anaerobes. *J Antimicrob Chemother* 25 (Suppl A): 19–24.
- Matsunaga N, Oki Y, Prigollini A (2003). A case of QT-interval prolongation precipitated by azithromycin. *N Z Med J* 116: U666.
- Mazzei T, Surrenti C, Novelli A *et al.* (1993). Pharmacokinetics of azithromycin in patients with impaired hepatic function. *J Antimicrob Chemother* 31 (Suppl E): 57–63.
- McLinn S (1996). A multicenter, double-blind comparison of azithromycin and amoxicillin/clavulanic acid in the treatment of paediatric patients with otitis media. *Pediatr Infect Dis J* 15: S20–3.
- Melese M, Alemayehu W, Lakew T *et al.* (2008). Comparison of annual and biannual mass antibiotic administration for elimination of infectious trachoma. *JAMA* 299: 778.
- Meyer AP, Bril-Bazuin C, Mattie H, van den Broek PJ (1993). Uptake of azithromycin by human monocytes and enhanced intracellular antibacterial activity against *Staphylococcus aureus*. *Antimicrob Agents Chemother* 37: 2318–22.
- Michalets EL, Williams CR (2000). Drug interactions with cisapride: clinical implications. *Clin Pharmacokinet* 39: 49–75.
- Milkovic-Kraus S, Macan J, Kanceljak-Marcan B (2007). Occupational allergic contact dermatitis from azithromycin in pharmaceutical workers: a case series. *Contact Dermatitis* 56: 99–102.
- Miller RS, Wongsrichanalai C, Buathong P *et al.* (2006). Effective treatment of uncomplicated *Plasmodium falciparum* malaria with azithromycin-quinine combinations: a randomized, dose-ranging study. *Am J Trop Med* 74: 401–06.
- Mitchell SJ, Engelman J, Kent CK *et al.* (2006). Azithromycin-resistant syphilis infection: San Francisco, California, 2000–2004. *Clin Infect Dis* 42: 337–45.
- Mori T, Aisa Y, Nakazato T *et al.* (2005). Tacrolimus-azithromycin interaction in a recipient of allogeneic bone marrow transplantation. *Transpl Int* 18: 757–8.

- Muhlestein JB, Anderson JL, Carlquist JF *et al.* (2000). Randomized secondary prevention trial of azithromycin in patients with coronary artery disease: primary clinical results of the ACADEMIC study. *Circulation* 102: 1755–60.
- Muirhead GJ, Faulkner S, Harness JA, Taubel J (2002). The effects of steady-state erythromycin and azithromycin on the pharmacokinetics of sildenafil in healthy volunteers. *Br J Clin Pharmacol* 53 (Suppl 1): S37–43.
- Muller HP, Holderrieth S, Burkhardt U, Hoffer U (2002). *In vitro* antimicrobial susceptibility of oral strains of *Actinobacillus actinomycetemcomitans* to seven antibiotics. *J Clin Periodontol* 29: 736–42.
- Nahata MC, Koranyi KI, Gadgil SD *et al.* (1993). Pharmacokinetics of azithromycin in pediatric patients after oral administration of multiple doses of suspension. *Antimicrob Agents Chemother* 37: 314–16.
- Nash KA, Indelied CB (1995). Genetic basis of macrolide resistance in *Mycobacterium avium* isolated from patients with disseminated disease. *Antimicrob Agents Chemother* 39: 2625–30.
- Niki Y, Kimura M, Miyashita N, Soejima R (1994). *In vitro* and *in vivo* activities of azithromycin, a new azalide antibiotic, against chlamydia. *Antimicrob Agents Chemother* 38: 2296–9.
- Noedl H, Krudsood S, Chalermratana K *et al.* (2006). Azithromycin combination therapy with artesunate or quinine for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults: a randomized, phase 2 clinical trial in Thailand. *Clin Infect Dis* 42: 1264–71.
- Noedl H, Krudsood S, Leowattana W *et al.* (2007). *In vitro* antimalarial activity of azithromycin, artesunate, and quinine in combination and correlation with clinical outcome. *Antimicrob Agents Chemother* 51: 651–6.
- Nouira S, Marghli S, Belghith M *et al.* (2001). Once daily oral oxfloracin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. *Lancet* 358: 2020–5.
- Novelli A, Fallani S, Cassetta MI *et al.* (2002). *In vivo* pharmacodynamic evaluation of clarithromycin in comparison to erythromycin. *J Chemother* 14: 584–90.
- O'Connor CM, Dunne MW, Pfeffer MA *et al.* (2003). Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. *JAMA* 290: 1459–66.
- O'Doherty B, Muller O (1998). Randomized, multicentre study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment of adults with mild to moderate community-acquired pneumonia. Azithromycin Study Group. *Eur J Clin Microbiol Infect Dis* 17: 828–33.
- Ohrst C, Willingmyre GD, Lee P *et al.* (2002). Assessment of azithromycin in combination with other antimalarial drugs against *Plasmodium falciparum* *in vitro*. *Antimicrob Agents Chemother* 46: 2518–24.
- O'Reilly T, Kunz S, Sande E *et al.* (1992). Relationship between antibiotic concentration in bone and efficacy of treatment of staphylococcal osteomyelitis in rats: azithromycin compared with clindamycin and rifampin. *Antimicrob Agents Chemother* 36: 2693–7.
- Ohtani H, Taninaka C, Hanada E *et al.* (2000). Comparative pharmacodynamic analysis of Q-T interval prolongation induced by the macrolides clarithromycin, roxithromycin, and azithromycin in rats. *Antimicrob Agents Chemother* 44: 2630–7.
- Okamoto H, Miyazaki S, Tateda K *et al.* (2000). Comparative *in vitro* activity of telithromycin (HMR 3647), three macrolides, amoxicillin, cefdinir and levofloxacin against gram-positive clinical isolates in Japan. *J Antimicrob Chemother* 46: 797–802.
- Oldfield III EC, Fessel WJ, Dunne MW *et al.* (1998). Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. *Clin Infect Dis* 26: 611–19.
- Page RL, Ruscin JM, Fish D, Lapointe M (2001). Possible interaction between intravenous azithromycin and oral cyclosporine. *Pharmacotherapy* 21: 1436–43.
- Pai MP, Graci DM, Amsden GW (2000). Macrolide drug interactions: an update. *Ann Pharmacother* 34: 495–513.
- Pajukanta R, Asikainen S, Saarela M *et al.* (1992). *In vitro* activity of azithromycin compared with that of erythromycin against *Actinobacillus actinomycetemcomitans*. *Antimicrob Agents Chemother* 36: 1241–3.
- Panpanich R, Lertrakarnnon P, Laopaiboon M (2004). Azithromycin for acute lower respiratory tract infections. *Cochrane Database Syst Rev* 4: CD001954.
- Parry CM, Ho VA, Phuonng le T *et al.* (2007). Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. *Antimicrob Agents Chemother* 51: 819–25.
- Parsad D, Pandhi R, Naggal R, Negi KS (2001). Azithromycin monthly pulse vs daily doxycycline in the treatment of acne vulgaris. *J Dermatol* 28: 1–4.
- Pascual A, Conejo MC, Garcia I, Perea EJ (1995). Factors affecting the intracellular accumulation and activity of azithromycin. *J Antimicrob Chemother* 35: 85–93.
- Periti P, Mazzei T, Mini E, Novelli A (1992). Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet* 23: 106–31.
- Periti P, Mazzei T, Mini E, Novelli A (1993). Adverse effects of macrolide antibacterials. *Drug Saf* 9: 346–64.
- Perronne C, Gikas A, Truffot-Pernot C *et al.* (1991). Activities of sparfloxacin, azithromycin, temafloxacin, and rifapentine compared with that of clarithromycin against multiplication of *Mycobacterium avium* complex within human macrophages. *Antimicrob Agents Chemother* 35: 1356–9.
- Peters DH, Friedel HA, McTavish D (1992). Azithromycin. A review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 44: 750–99.
- Phaff SJ, Tiddens HA, Verbrugh HA, Ott A (2005). Macrolide resistance of *Staphylococcus aureus* and *Haemophilus* species associated with long-term azithromycin use in cystic fibrosis. *J Antimicrob Chemother* 57: 741–6.
- Phimda K, Hoontrakul S, Suttinont C *et al.* (2007). Doxycycline versus azithromycin in treatment of leptospirosis and scrub typhus. *Antimicrob Agents Chemother* 51: 3259–63.
- Plouffe JF, Schwartz DB, Kolokathis A *et al.* (2000). Clinical efficacy of intravenous followed by oral azithromycin monotherapy in hospitalized patients with community acquired pneumonia. The Azithromycin Intravenous Clinical Trials. *Antimicrob Agents Chemother* 44: 1796–802.
- Plouffe JF, Breiman RF, Fields BS *et al.* (2003). Azithromycin in the treatment of *Legionella pneumonia* requiring hospitalization. *Clin Infect Dis* 37: 1475–80.
- Rahman M, Shoma S, Rashid H *et al.* (2007). Increasing spectrum in antimicrobial resistance of *Shigella* isolates in Bangladesh: resistance to azithromycin and ceftriaxone and decreased susceptibility to ciprofloxacin. *J Health Popul Nutr* 25: 158–67.
- Rakita RM, Jacques-Palaz K, Murray BE (1994). Intracellular activity of azithromycin against bacterial enteric pathogens. *Antimicrob Agents Chemother* 38: 1915–21.
- Ram FS, Rodriguez-Rosin R, Grandados-Navarrete A *et al.* (2006). Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2: CD004403.
- Ramsey PS, Vauls MB, Vasdev GM *et al.* (2003). Maternal and transplacental pharmacokinetics of azithromycin. *Am J Obstet Gynecol* 188: 714–18.
- Rapeport WG, Dewland PM, Muirhea DC, Forster PL (1991). Lack of an interaction between azithromycin and carbamazepine. In: *Proceedings and Abstracts of the British Pharmacological Society. Clinical Pharmacology Section*. London: University College/Sandoz Institute for Medical Research, 551P.
- Raulston JE (1994). Pharmacokinetics of azithromycin and erythromycin in human endometrial epithelial cells and in cells infected with *Chlamydia trachomatis*. *J Antimicrob Chemother* 34: 765–76.
- Rehg JE (1991). Activity of azithromycin against cryptosporidia in immunosuppressed rats. *J Infect Dis* 163: 1293–6.
- Ressner RA, Griffith ME, Beckius ML *et al.* (2008). Antimicrobial susceptibilities of geographically diverse clinical human isolates of *Leptospira*. *Antimicrob Agents Chemother* 52: 2750–4.
- Retsema J, Girard A, Schelkly W *et al.* (1987). Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. *Antimicrob Agents Chemother* 31: 1939–47.
- Riedner G, Rustzoka M, Todd J *et al.* (2005). Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med* 353: 1236–44.
- Roden DM (2008). Cellular basis of drug-induced torsades de pointes. *Br J Pharmacol* 154: 1502.

- Rolin O, Bouanchaud DH (1989). [Comparison of the *in vitro* post-antibiotic effect of C14 macrolides (erythromycin and roxithromycin) and C16 macrolides (josamycin and spiramycin) against *Staphylococcus aureus*]. *Pathol Biol (Paris)* 37: 375–7.
- Rosenfeld RM, Andes D, Bhattacharyya N *et al.* (2007). Clinical practice guidelines: adult sinusitis. *Otolaryngol Head Neck Surg* 137 (3 Suppl): S1–31.
- Ross BD, Gross EM (2000). Irreversible sensorineural hearing loss as a result of azithromycin ototoxicity: a case report. *Ann Otol Rhinol Laryngol* 109: 435–7.
- Russo V, Puzio G, Siniscalchi N (2006). Azithromycin-induced QT prolongation in elderly patient. *Acta Biomed* 77: 30–2.
- Rylander M, Hallander HO (1988). *In vitro* comparison of the activity of doxycycline, tetracycline, erythromycin and a new macrolide, CP 62993, against *Mycoplasma pneumoniae*, *Mycoplasma hominis* and *Ureaplasma urealyticum*. *Scand J Infect Dis Suppl* 53: 12–17.
- Saba J, Morlat P, Raffi F *et al.* (1993). Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis* 12: 853–6.
- Saha D, Karim MM, Khan-WA *et al.* (2006). Single-dose azithromycin for the treatment of cholera in adults. *N Engl J Med* 354: 2452–242.
- Sarkar M, Wodland CC, Koren G, Einarsson AR (2006). Pregnancy outcome following gestational exposure to azithromycin. *BMC Pregnancy Childbirth* 30: 18.
- Samra Z, Rosenberg S, Soffer Y, Dan M (2001). *In vitro* susceptibility of recent clinical isolates of *Chlamydia trachomatis* to macrolides and tetracyclines. *Diagn Microbiol Infect Dis* 39: 177–9.
- Sanders JW, Frenck RW, Putnam SD *et al.* (2007). Azithromycin and loperamide are comparable to levofloxacin and loperamide for the treatment of travelers' diarrhoea in United States military personnel in Turkey. *Clin Inf Dis* 45: 294–301.
- Schaad UB (1993). Multicentre evaluation of azithromycin in comparison with co-amoxiclav for the treatment of acute otitis media in children. *J Antimicrob Chemother* 31 (Suppl E): 81–8.
- Schachter J, West SK, Mabey D *et al.* (1999). Azithromycin in control of trachoma. *Lancet* 354: 630–5.
- Schentag JJ, Ballow CH (1991). Tissue-directed pharmacokinetics. *Am J Med* 91: 5S–11S.
- Schentag JJ, Klugman KP, Yu VL *et al.* (2007). *Streptococcus pneumoniae* bacteraemia: Pharmacodynamic correlations with outcome and macrolide resistance – a controlled study. *Int J Antimicrob Agents* 30: 264–9.
- Schmedes A, Lildholdt T, Schouenborg P, Eriksen DW (1998). Azithromycin concentrations and microbiology of tonsils during weekly medication in patients with recurrent tonsillitis. *Clin Drug Investig* 15: 467–72.
- Schwab JC, Cao Y, Slowik MR, Joiner KA (1994). Localization of azithromycin in *Toxoplasma gondii*-infected cells. *Antimicrob Agents Chemother* 38: 1620–7.
- Seral C, Van Bambeke F, Tulkenes PM (2003a). Quantitative analysis of gentamicin, azithromycin, telithromycin, ciprofloxacin, moxifloxacin, and oritavancin (LY333328) activities against intracellular *Staphylococcus aureus* in mouse J774 macrophages. *Antimicrob Agents Chemother* 47: 2283–92.
- Seral C, Carryn S, Tulkenes PM, Van Bambeke F (2003b). Influence of P-glycoprotein and MRP efflux pump inhibitors on the intracellular activity of azithromycin and ciprofloxacin in macrophages infected by *Listeria monocytogenes* or *Staphylococcus aureus*. *J Antimicrob Chemother* 51: 1167–73.
- Shrader SP, Fermo JD, Dzikowski AL (2004). Azithromycin and warfarin interaction. *Pharmacotherapy* 24: 945–9.
- Shepard RM, Falkner FC (1990). Pharmacokinetics of azithromycin in rats and dogs. *J Antimicrob Chemother* 25 (Suppl A): 49–60.
- Silva FM, Eisig JN, Teixeira AC *et al.* (2008). Short-term triple therapy with azithromycin for *Helicobacter pylori* eradication: low cost, high compliance, but low efficacy. *BMC Gastroenterol* 8: 20.
- Sinialo J, Mattila K, Valtonen V *et al.* (2002). Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-Q-wave coronary syndrome. *Circulation* 105: 1555–60.
- Slaney L, Chubb H, Ronald A, Brunham R (1990). *In-vitro* activity of azithromycin, erythromycin, ciprofloxacin and norfloxacin against *Neisseria gonorrhoeae*, *Haemophilus ducreyi*, and *Chlamydia trachomatis*. *J Antimicrob Chemother* 25 (Suppl A): 1–5.
- Smith MD, Vinh DX, Nguyen TT *et al.* (1995). *In vitro* antimicrobial susceptibilities of strains of *Yersinia pestis*. *Antimicrob Agents Chemother* 39: 2153–4.
- Solans A, Izquierdo I, Donado E *et al.* (2008). Pharmacokinetic and safety profile of rupatadine when coadministered with azithromycin at steady-state levels: a randomized, open-label, two-way, crossover, Phase 1 study. *Clin Ther* 30: 1639–50.
- Soley CA, Arguedas A (2005). Single-dose azithromycin for the treatment of children with acute otitis media. *Expert Rev Anti Infect Ther* 3: 707–17.
- Solomon AW, Holland MJ, Alexander ND *et al.* (2004). Mass treatment with single-dose azithromycin for trachoma. *N Engl J Med* 351: 1962–71.
- Solomon AW, Harding-Esch E, Alexander ND *et al.* (2008). Two doses of azithromycin to eliminate trachoma in a Tanzanian community. *N Eng J Med* 358: 1870–1.
- Soni N, Harrington JW, Weiss R *et al.* (2004). Recurrent acute interstitial nephritis induced by azithromycin. *Pediatr Infect Dis J* 23: 965–6.
- Southern KW, Barker PM, Solis A (2004). Macrolide antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2: CD002203.
- Springer B, Stockman L, Tescher K *et al.* (1996). Two-laboratory collaborative study on identification of mycobacteria: molecular versus phenotypic methods. *J Clin Microbiol* 34: 29.
- Stamler DA, Edelstein MA, Edelstein PH (1994). Azithromycin pharmacokinetics and intracellular concentrations in *Legionella pneumophila*-infected and uninfected guinea pigs and their alveolar macrophages. *Antimicrob Agents Chemother* 38: 217–22.
- Steingrimsson O, Olafsson JH, Thorarinnsson H *et al.* (1994). Single dose azithromycin treatment of gonorrhoea and infections caused by *C. trachomatis* and *U. urealyticum* in men. *Sex Transm Dis* 21: 43–6.
- Steinkamp G, Schmitt-Grohe S, Doring G *et al.* (2008). Once-weekly azithromycin in cystic fibrosis with chronic *Pseudomonas aeruginosa* infection. *Respir Med* 102: 1643–53.
- Stock I (2005). Natural antimicrobial susceptibility patterns of *Kluyvera ascorbata* and *Kluyvera cryocrescens* strains and review of the clinical efficacy of antimicrobial agents used for the treatment of *Kluyvera* infections. *J Chemother* 17: 143–60.
- Stock I, Wiedemann B (2001). Natural antimicrobial susceptibilities of *Plesiomonas shigelloides* strains. *J Antimicrob Chemother* 48: 803–11.
- Stock I, Burak S, Wiedemann B (2004). Natural antimicrobial susceptibility patterns and biochemical profiles of *Leclercia adecarboxylata* strains. *Clin Microbiol Infect* 10: 724–33.
- Sullivan B, Coyle W, Nemeč R, Dunteman T (2002). Comparison of azithromycin and clarithromycin in triple therapy regimens in triple therapy regimens for the eradication of *Helicobacter pylori*. *Am J Gastroenterol* 97: 2536–9.
- Sunakawa K, Farrell DJ (2007). Mechanisms, molecular and sero-epidemiology of antimicrobial resistance in bacterial respiratory pathogens isolated from Japanese children. *Ann Clin Microbiol Antimicrob* 6: 7.
- Swainston HT, Keam SJ (2007). Azithromycin extended release: a review of its use in the treatment of acute bacterial sinusitis and community-acquired pneumonia in the US. *Drugs* 67: 773–92.
- Swanson RN, Lainez-Ventosa A, De Salvo MC *et al.* (2005). Once-daily azithromycin for 3 days compared with clarithromycin for 10 days for acute exacerbation of chronic bronchitis: a multicenter, double-blind, randomized study. *Treat Respir Med* 4: 31–9.
- Tamm M, Todisco T, Feldman C *et al.* (2007). Clinical and bacteriological outcomes in hospitalised patients with community-acquired pneumonia treated with azithromycin plus ceftriaxone, or ceftriaxone plus clarithromycin or erythromycin: a prospective, randomised, multicentre study. *Clin Microbiol Infect* 13: 162–71.
- Taylor DE, Chang N (1991). *In vitro* susceptibilities of *Campylobacter jejuni* and *Campylobacter coli* to azithromycin and erythromycin. *Antimicrob Agents Chemother* 35: 1917–8.
- Taylor WR, Richie TL, Fryauff DJ *et al.* (2003). Tolerability of azithromycin as malaria prophylaxis in adults in Northeast Papua, Indonesia. *Antimicrob Agents Chemother* 47: 2199–203.
- Thalhammer F, Hollenstein UM, Locker GJ, Janata K (1998). Azithromycin-related toxic effects of digitoxin. *Br J Clin Pharmacol* 45: 91–2.

- Threlfall EJ, de Pinna E, Day M *et al.* (2008). Alternatives to ciprofloxacin use for enteric fever, United Kingdom. *Emerg Inf Dis* 14: 860–1.
- Timurkaynak F, Can F, Azap OK *et al.* (2006). *In vitro* activities of non-traditional antimicrobials alone or in combination against multidrug-resistant strains of *Pseudomonas aeruginosa* and *Actinobacter baumannii* isolated from intensive care units. *Int J Antimicrob Agents* 27: 224–8.
- Tissi L, von Hunolstein C, Mosci P *et al.* (1995). *In vivo* efficacy of azithromycin in treatment of systemic infection and septic arthritis induced by type IV group B *Streptococcus* strains in mice: Comparative study with erythromycin and penicillin G. *Antimicrob Agents Chemother* 39: 1938–47.
- Tiwari T, Murphy TV, Moran J (2005). Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis. *MMWR Recomm Rep* 54: 1–16.
- Treadway G, Pontani D, Reisman A (2002). The safety of azithromycin in the treatment of adults with community-acquired respiratory tract infections. *Int J Antimicrob Agents* 19: 189–94.
- Tribble DR, Sanders JW, Pang LW *et al.* (2007). Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. *Clin Infect Dis* 44: 338–46.
- Tseng AL, Dolovich L, Salit IE (1997). Azithromycin-related ototoxicity in patients infected with human immunodeficiency virus. *Clin Infect Dis* 24: 76–7.
- Uzun C, Koten M, Adali MK *et al.* (2001). Reversible ototoxic effect of azithromycin and clarithromycin on transiently evoked otoacoustic emissions in guinea pigs. *J Laryngol Otol* 115: 622–8.
- Vaara M (1993). Outer membrane permeability barrier to azithromycin, clarithromycin, and roxithromycin in gram-negative enteric bacteria. *Antimicrob Agents Chemother* 37: 354–6.
- Vergis EN, Indorf A, File TM *et al.* (2000). Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients: a prospective, randomized, multicenter trial. *Arch Intern Med* 160: 1294–300.
- Von Rosensteil NA, Adam D (1995). Macrolide antibacterials. Drug interactions of clinical significance. *Drug Saf* 13: 105–22.
- Wallace Jr RJ, Brown BA, Griffith DE *et al.* (1994). Initial clarithromycin monotherapy for *Mycobacterium avium*-intracellulare complex lung disease. *Am J Respir Crit Care Med* 149: 1335–41.
- Wallace MR, Miller LK, Nguyen MT, Shields AR (1994). Ototoxicity with azithromycin. *Lancet* 343: 241.
- Walsh M, Kappus EW, Quinn TC (1987). *In vitro* evaluation of CP-62,993, erythromycin, clindamycin, and tetracycline against *Chlamydia trachomatis*. *Antimicrob Agents Chemother* 31: 811–12.
- Watson C, Alp NJ (2008). Role of *Chlamydia pneumoniae* in atherosclerosis. *Clin Sci (Lond)* 114: 509–31.
- Watt B, Rayner A, Harris G (1996a). Comparative activity of azithromycin against clinical isolates of mycobacteria. *J Antimicrob Chemother* 38: 539–42.
- Watt G, Chouriyagune C, Ruangweerayud R *et al.* (1996b). Scrub typhus infections poorly responsive to antibiotics in northern Thailand. *Lancet* 348: 86–9.
- Wells BJ, Mainous 3rd AG, Dickerson LM (2004). Antibiotics for the secondary prevention of ischaemic heart disease: a meta-analysis of randomised controlled trials. *Arch Intern Med* 164: 2156–61.
- Wiese MD, Cosh DG (1999). Raised INR with concurrent warfarin and azithromycin. *Aust J Hosp Pharm* 29: 274–8.
- Wildfeuer A, Laufen H, Leitold M, Zimmermann T (1993). Comparison of the pharmacokinetics of three-day and five-day regimens of azithromycin in plasma and urine. *J Antimicrob Chemother* 31 (Suppl E): 51–6.
- Williams D, Ponte CD (2003). Warfarin-associated hypothermia: an unusual presentation. *Am J Health-Syst Pharm* 60: 274–8.
- Williams JD, Maskell JP, Shain H *et al.* (1992). Comparative *in-vitro* activity of azithromycin, macrolides (erythromycin, clarithromycin and spiramycin) and streptogramin RP 59500 against oral organisms. *J Antimicrob Chemother* 30: 27–37.
- Woldtvedt BR, Cahoon CL, Bradley LA, Mille SJ (1998). Possible increased anticoagulation effect of warfarin induced by azithromycin. *Ann Pharmacother* 32: 269–70.
- Workowski KA, Berman SM (2006). Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep* 55: 1–94.
- World Health Organization (2005). *Guidelines for the control of shigellosis, including epidemics due to Shigella dysenteriae 1*. Geneva: World Health Organization.
- World Health Organization (2006). *Guidelines for the treatment of malaria*. Geneva: World Health Organization.
- Wormser GP, Dattwyler RJ, Shapiro ED *et al.* (2006). The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 43: 1089–134.
- Zervos M, Martinez FJ, Amsden GW *et al.* (2007). Efficacy and safety of 3-day azithromycin versus 5-day moxifloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis. *Int J Antimicrob Agents* 29: 56–61.
- Zhanel GG, Dueck M, Hoban DJ *et al.* (2001). Review of macrolides and ketolides: focus on respiratory tract infections. *Drugs* 61: 443–98.
- Zhanel GG, DeCorby M, Noreddin A *et al.* (2003a). Pharmacodynamic activity of azithromycin against macrolide-susceptible and -resistant *Streptococcus pneumoniae* simulating clinically achievable free serum, epithelial lining fluid and middle ear fluid concentrations. *J Antimicrob Chemother* 52: 83–8.
- Zhanel GG, Palatnick L, Nichol KA *et al.* (2003b). Antimicrobial resistance in *Haemophilus influenzae* and *Moraxella catarrhalis* respiratory tract isolates: results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002. *Antimicrob Agents Chemother* 47: 1875–81.
- Zouboulis CC, Piquero-Martin J (2003). Update and future of systemic acne treatment. *Dermatology* 206: 37–53.