KUCERS' THE USE OF ANTIBIOTICS

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

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61 Clarithromycin

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1. DESCRIPTION

Clarithromycin (CAS number: 81103-11-9) is the 6-0-methyl derivative of erythromycin (Morimoto *et al.*, 1984; Fernandes *et al.*, 1986). The replacement of the hydroxyl substituant by a methoxy group in position 6 renders the molecule resistant to acidic hydrolysis improving its oral bioavailability compared with erythromycin (see Chapter 59, Erythromycin). The empirical formula is $C_{38}H_{69}NO_{13}$ and the molecular weight is 748.0; the molecular structure is shown in Figure 61.1.

In general, clarithromycin has the same spectrum and the same therapeutic indications as erythromycin (Amsden, 1996). The *in vitro* activity of clarithromycin against most aerobic microorganisms is equal to or twice that of erythromycin, except for *Haemophilus influenzae* for which it is half as active (Fernandes *et al.*, 1986; Hardy *et al.*, 1988a). Owing to its high intrinsic activity, it is the macrolide of choice for *Helicobacter pylori* gastritis and *Mycobacterium avium* complex (MAC) infection. Moreover, it is associated with an improved pharmacokinetic profile – higher oral bioavailability, longer half-life, higher tissue accumulation, and lower degree of interaction with CYP450 (Periti *et al.*, 1992; Fraschini *et al.*, 1993). In humans, clarithromycin has four metabolites, the most important of which is 14-hydroxy clarithromycin. This metabolite shows antimicrobial activity with MICs usually one or two dilutions lower than those of clarithromycin (Logan *et al.*, 1991; Martin *et al.*, 2001).

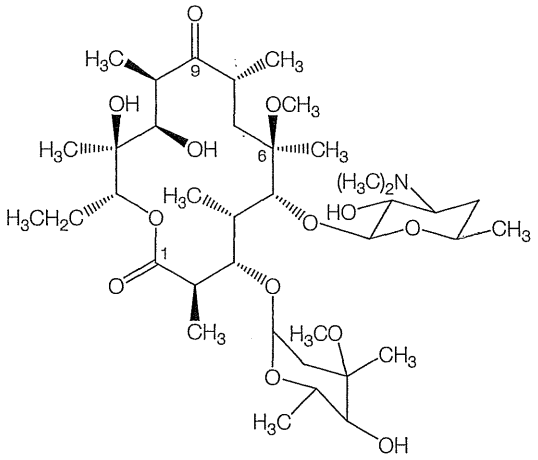

Figure 61.1 Molecular structure of clarithromycin. Chemical stability in acid medium is a result of the replacement of the hydroxyl group in position 6 of erythromycin by a methoxy group.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Macrolides are characterized by a moderately broad spectrum of activity, which includes most Gram-positives, 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 61.1 lists the susceptibilities observed for wild-type strains of the most relevant target organisms.

Gram-positive aerobic bacteria

Staphylococcus aureus, including beta-lactamase-producing strains, is susceptible to clarithromycin and its 14-hydroxy metabolite, but, similar to erythromycin, methicillin-resistant strains are usually resistant. The same is true for coagulase-negative staphylococci. Group A hemolytic streptococci, streptococci of Groups B, C and G, *Streptococcus pneumoniae*, and *S. viridans* are also susceptible. Similar to erythromycin, *Enterococcus faecalis* is less susceptible to clarithromycin. In general, most of these organisms are about twice as susceptible to clarithromycin as to erythromycin, and they are about equally susceptible to the hydroxy- metabolite and erythromycin (Barry *et al.*, 1987; Benson *et al.*, 1987; Eliopoulos *et al.*, 1987; Floyd-Reising *et al.*, 1987; Neu, 1991; Goldstein and Citron, 1993; Hardy, 1993).

Clarithromycin is active against *Listeria monocytogenes* and *Corynebacterium* spp., except *C. jeikeium*, which is resistant (Benson *et al.*, 1987; Hardy *et al.*, 1988a; Bauer and Hof, 1992; Goldstein and Citron, 1993).

Gram-positive anaerobic bacteria

The anaerobic Gram-positive cocci such as *Peptostreptococcus* spp. are usually moderately clarithromycin susceptible. The same is true for *Clostridium* spp. and *Propionibacterium acnes* (Fernandes *et al.*, 1986; Fass, 1993; Goldstein and Citron, 1993).

Gram-negative bacteria

Clarithromycin is active against *Neisseria meningitidis* and *N. gonorrhoeae* (Barry *et al.*, 1987; Eliopoulos *et al.*, 1987), *Bordetella pertussis* and *B. parapertussis* (Hardy, 1993), *Moraxella catarrhalis*, *Pasteurella multocida* (Eliopoulos *et al.*, 1987; Fass, 1993), *Bartonella* spp. (Dörbecker *et al.*, 2006), and *Campylobacter jejuni* (Bakeli *et al.*, 2008). Most strains of *C. coli* and *C. fetus* are also susceptible (Endtz *et al.*, 1993; Sanchez *et al.*, 1994).

Haemophilus influenzae is only moderately susceptible to clarithromycin (MICs 2–8 mg/l), but its metabolite, 14-hydroxy-clarithromycin, has MICs that are one dilution lower. The combination of the drug with its metabolite is bactericidal and synergistic against *H. influenzae*

Table 61.1 MICs (μg/ml) of clarithromycin for key pathogens, compared with susceptibility breakpoints

Bacteria	Wild-type strains (EUCAST distributions of MIC)			Clinical isolates				Breakpoints		Resistance issues	References
	Range	MIC_{50}	MIC_{90}	Study period	Range	MIC_{50}	MIC_{90}	CLSI Bkpt (S ≤/R ≥)	EUCAST Bkpt (S ≤/R >)		
Staphylococcus aureus (MSSA)	0.064–0.125	0.064	0.125	2002 (Italy)		0.5	>32	2/8	1/2		Noviello *et al.*, 2003
Staphylococcus aureus (MRSA)	0.064–0.125	0.064	0.125	2002 (Italy)		>32	>32	2/8	1/2	HA-MRSA frequently multiresistant	Noviello *et al.*, 2003
Streptococcus pneumoniae	0.016–0.125	0.032	0.064	1999–2000 (Asia)		32	>32	0.25/1	0.25/0.5	High prevalence in many countries; often multiresistant strains	Felmingham *et al.*, 2002
				1999–2000 (Europe)		0.03	32				Felmingham *et al.*, 2002
				1999–2000 (North America)		0.06	8				Felmingham *et al.*, 2002
Streptococcus pyogenes	0.016–0.125	0.032	0.064	1999–2000 (Europe)		0.03	0.06	0.25/1	0.25/0.5		Canton *et al.*, 2002
Haemophilus influenzae	0.25–16	8	16	2002–2003 (UK)	0.5–128	8	16	8/32	1/32		Morrissey *et al.*, 2005
Moraxella catarrhalis	0.008–0.064	0.032	0.064	2002–2003 (UK)	0.015–0.125	0.03	0.03		0.25/0.5		Morrissey *et al.*, 2005
Legionella pneumophila	0.25–0.5	0.25	0.25	1999–2004 (Europe-USA)	≤0.25–0.5	≤0.25	≤0.25				Dunbar and Farrell, 2007
Helicobacter pylori				2004–2005 (Japan)	<0.016–128	0.06	32	0.25/1		Prevalence of resistance is increasing worldwide	Kobayashi *et al.*, 2007
Chlamydia trachomatis				1997–1999 (Israel)	0.008–0.015	0.015	0.015				Samra *et al.*, 2001
Chlamydophila pneumoniae				USA	0.015–0.06	0.03	0.06				Malay *et al.*, 2002
Mycobacterium avium and complex				Japan	0.25–16						Kobashi *et al.*, 2006

Bkpt: break point; CLSI: Clinical Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; HA-MRSA: hospital-acquired methicillin-resistant *S. aureus* MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*.

(Hardy *et al.*, 1990; Hoover *et al.*, 1992). *Haemophilus parainfluenzae* is moderately susceptible (Benson *et al.*, 1987), but *H. ducreyi* is very susceptible (MICs 0.002–0.06 mg/l) (Dangor *et al.*, 1988).

Clarithromycin is one of the most active macrolides against *H. pylori* (Hardy *et al.*, 1988b) and *L. pneumophila* (Eliopoulos *et al.*, 1987; Reda *et al.*, 1994; Stout *et al.*, 2005). Its activity against *Legionella* spp. is enhanced by its 14-hydroxy metabolite (Jones *et al.*, 1990). *Vibrio* spp. are moderately susceptible and the Enterobacteriaceae and *Pseudomonas aeruginosa* are resistant (Benson *et al.*, 1987; Chin *et al.*, 1987).

Gram-negative anaerobe bacteria

Some Gram-negative anaerobes such as *Prevotella melaninogenica* may be moderately clarithromycin susceptible, but *Bacteroides fragilis* and other members of the *B. fragilis* group and *Fusobacterium* spp. are usually resistant (Chin *et al.*, 1987; Hardy *et al.*, 1988a; Fass, 1993).

Other pathogens

Clarithromycin is active against *Mycobacteria* spp., with MICs from 1.3 to 10 mg/l for *M. tuberculosis* (Gorzynski *et al.*, 1989), from 1 to 8 mg/l for *M. avium* complex (Brown *et al.*, 1992a), and of 0.25 mg/l for *M. paratuberculosis* (Rastogi *et al.*, 1992). The drug is also quite active against *M. fortuitum*, *M. chelonae*, and *M. chelonae*-like organisms (Brown *et al.*, 1992b), *M. gordonae*, *M. scrofulaceum*, *M. szulgai*, *M. kansasii*, *M. haemophilum*, but *M. simiae* is relatively resistant (Biehle and Cavalieri, 1992; Brown *et al.*, 1992a; Bernard *et al.*, 1993; Alcaide *et al.*, 2004; da Silva Telles *et al.*, 2005). Clarithromycin is also rapidly bactericidal against *M. leprae* growing in mouse foot pads (Gelber *et al.*, 1991).

Clarithromycin is usually more active than erythromycin against *C. trachomatis* (Segreti *et al.*, 1987; Samra *et al.*, 2001) and *Chlamydophila pneumoniae* (Roblin *et al.*, 1994). It is as effective as erythromycin against *Mycoplasma pneumoniae* and *Ureaplasma urealyticum* (Waites *et al.*, 1988). However, *Mycoplasma hominis* has *in vitro* resistance to macrolides (Samra *et al.*, 2002). Clarithromycin is active *in vitro* against *Borrelia burgdorferi* (with MICs lower than doxycycline) (Dever *et al.*, 1993), *Rickettsia rickettsii*, *R. conorii*, *R. israeli*, *Coxiella burnetii* (Maurin and Raoult, 1993), and *Leptospira* spp. (Ressner *et al.*, 2008). The drug also shows activity *in vivo* against *Treponema pallidum* in hamsters (Alder *et al.*, 1993), and *T. gondii* infections in mice and infected cells (Chang and Pechere, 1988; Chang *et al.*, 1988).

2b. Emerging resistance and cross-resistance

Resistance to macrolides has become a major issue for most of the bacteria originally described as susceptible, including *Staphylococcus* spp., *Streptococcus* spp., *Bacteroides* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Lactobacillus* spp., *M. pneumoniae*, *Campylobacter* spp., *Corynebacterium diphtheriae*, and *Propionibacterium* spp., as well as many members of the *Enterobacteriaceae* (Leclercq and Courvalin, 1991; Goldstein and Garau, 1994; Bartlett, 1997; Doern, 2006). 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 – these are reviewed in Chapter 59, Erythromycin.

Therapy with clarithromycin has been shown to increase macrolide resistance in oropharyngeal flora (Aberg *et al.*, 2001; Berg *et al.*, 2004; Kasahara *et al.*, 2005; Malhotra-Kumar *et al.*, 2007).

Resistance among strains of *H. pylori* appears to be increasing and is often related to previous use of macrolides (Cars *et al.*, 2001; Koletzko *et al.*, 2006). Resistance is due to a point mutation in the 23S RNA; A2143G and A2142G are the most common (Mégraud, 2004). The latter demonstrates cross-resistance to other macrolides and lincosamides. Strains with these mutations have been shown to have higher growth rates *in vitro*. The A2143G mutation appears to be associated with a very low eradication rate of *H. pylori* with standard triple therapy (Taylor, 2000; De Francesco *et al.*, 2006; see below under 7. Clinical uses of the drug).

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

Clarithromycin is mainly administered by the oral route, at a daily dose of 500–1000 mg divided into two doses for immediate release formulations. Two adult formulations have been developed – namely immediate-release tablets (250 or 500 mg) and extended-release tablets (500 mg). The extended-release formulation should be taken with food as bioavailability is reduced under fasting conditions (Guay *et al.*, 2001). Immediate-release tablets may be taken with or without food. The dose and duration of therapy is dependent on its clinical use (see below under 7. Clinical uses of the drug).

Parenteral administration

Clarithromycin is also available for i.v. administration in some countries (500 mg vials), at a daily dose of 1000 mg divided in two administrations. It should be administered into one of the larger proximal veins as an infusion over 60 minutes, using a solution concentration of about 2 mg/ml.

Intravitreal administration

Intravitreal clarithromycin, in doses up to 1 mg has been shown to be nontoxic in a rabbit model (Unal *et al.*, 1999).

4b. Newborn infants and children

Pediatric dosage (for granules to be reconstituted as an oral suspension) is 7.5–15 mg/kg, divided in two administrations. Granules may be taken without or with food.

4c. Altered dosages

Impaired renal function

In patients with severe renal impairment (creatinine clearance (CL_{Cr}) <30 ml/min) with or without co-existing hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate. Dose reduction should be as follows: CCl 10–50 ml/min, 75%; <10 ml/min, 50–75%. No dose reduction is necessary for patients

undergoing continuous ambulatory peritoneal dialysis (CAPD) or continuous arteriovenous hemofiltration (CAVH) or continuous venovenous hemofiltration (CVVH). Patients undergoing hemodialysis should be dosed after dialysis, although there are few detailed data in this situation (Aronoff *et al.*, 2007; Gilbert *et al.*, 2009).

Impaired hepatic function

Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function (Gilbert *et al.*, 2009).

The elderly

The pharmacokinetics of macrolides are modified in elderly patients (Chu *et al.*, 1992c). Dosage adjustment for clarithromycin is usually not required with the conventional dose, but closer than usual clinical monitoring of the older patient has been advocated (Periti *et al.*, 1989).

5. PHARMACOKINETICS AND PHARMACODYNAMICS

The main pharmacokinetic properties of clarithromycin are summarized in Table 61.2.

5a. Bioavailability

Clarithromycin is acid stable and is well absorbed after oral administration (t_{max}, 2–3 hours; bioavailability, 55%) (Davey, 1991). After absorption, approximately half of the absorbed dose is converted to its active metabolite 14-hydroxy-clarithromycin. The peak serum level of clarithromycin and its metabolite are 0.78 and 0.65 mg/l after a dose of 250 mg and 2.12 and 1.0 mg/l after a dose of 500 mg, respectively. The pharmacokinetics of clarithromycin is apparently not linear, with peak serum level of the drug itself increasing to more than double the value after doubling the dose. This is because of saturation of the metabolic pathway for the production of the metabolite (Rodvold and Piscitelli, 1993). Clarithromycin is approximately 70% bound to serum proteins, but binding decreases with increasing concentration of clarithromycin (Davey, 1991; Chu *et al.*, 1992a).

In healthy volunteers, after administration of 1 g of the extended release formulation, a serum peak level of 2–3 mg/l was achieved after 5–8 hours for the drug, and 0.6 mg/l after 6–9 hours for the active metabolite. The 24-hour AUC is similar to that obtained after a twice-daily administration of 500 mg of the immediate release formulation. However, a reduction of 30% of the AUC is observed for the extended-release formulation when administered under fasting conditions (Guay *et al.*, 2001).

When given in combination with omeprazole 40 mg, the serum peak level and the AUC of clarithromycin are increased by about 10% and 15%, respectively; its concentrations are also increased in the gastric mucus and tissue (Gustavson *et al.*, 1995).

In children, after a 7.5 mg/kg dose of clarithromycin suspension, the peak serum level at 3 hours was approximately 4.0 mg/l. The peak level of the metabolite, attained in 4 hours, was approximately 1.0 mg/l (Gan *et al.*, 1992; Guay and Craft, 1993).

Table 61.2 Pharmacokinetic parameters of clarithromycin. From: Peters and Clissold (1992), Fraschini *et al.* (1993) and Guay *et al.* (2001).

Pharmacokinetic parameter	Clarithromycin (500 mg bid immediate-release formulation)	Clarithromycin (1000 mg qd extended-release formulation)
C_{max} (mg/l) drug	3–4	2–3
C_{max} (mg/l) metabollite	1	0.8
T_{max} (hours)	2–3	5–8
$T_{1/2}$ (hours)	5–7	
Vd (l/kg)	3–4	
Bioavailability (%)	55	
Protein binding (%)	42–50	
AUC (mg/l h)	46	42

The key pharmacokinetic parameters of clarithromycin are summarized in Table 61.2.

5b. Drug distribution

Clarithromycin readily penetrates in fluids and tissues, where it reaches concentrations 2–10 times higher than in serum. The penetration of clarithromycin is considered as excellent, with high-tissue accumulation in the gastric tissue (Gustavson *et al.*, 1995; Nakamura *et al.*, 2003), the lung (Fish *et al.*, 1994; Rodvold *et al.*, 1997; Kikuchi *et al.*, 2008), the tonsil, and the gingiva (Burrell and Walters, 2008), and good accumulation in the middle ear fluid effusion (Sundberg and Cederberg, 1994; Gan *et al.*, 1997), the sinus fluid (Margaritis *et al.*, 2007), the sputum (Tsang *et al.*, 1994), the prostate (Giannopoulos *et al.*, 2001), and the eye (Al-Sibai *et al.*, 1998). Although these fluid concentrations all technically exceed the minimum inhibitory concentrations of most common pathogens, the clinical relevance of such analyses has been questioned based on the pharmacokinetic–pharmacodynamic parameters of drugs such as clarithromycin (Mouton *et al.*, 2008). Like other macrolides, clarithromycin enters macrophages and polymorphonuclear cells and accumulates inside eukaryotic cells (Anderson *et al.*, 1988; Mor *et al.*, 1994; Seral *et al.*, 2003).

Patients receiving the drug in a dosage of 250 mg orally 12-hourly reached peak tissue levels 4 hours after administration, and the mean peak concentrations in nasal mucosa and in tonsil were 8.32 and 6.47 μg/g, respectively (Fraschini *et al.*, 1991). Patients who were to undergo lung resection were given clarithromycin 500 mg orally every 12 hours for a minimum of five doses and lung resection was performed approximately 4 hours after the final dose. The concentrations of the drug and its 14-hydroxymetabolite in the lung tissue at this time averaged 54.3 and 5.12 μg/g, respectively, with a mean calculated ratio of concentrations of the parent to metabolite being 11.3 in lung tissue and 2.4 in plasma (Fish *et al.*, 1994). The drug is also concentrated in epithelial lining fluid and in alveolar cells (Conte *et al.*, 1995). The concentrations of clarithromycin in alveolar epithelial lining fluid and alveolar marophages 3 hours after oral administration of 200 mg were 4.84 and 10.7 mg/l, respectively, with an AUC (0–10 hours) of 7.37 mg/l h in the bronchial epithelial lining fluid, a value more than three times higher than that measured in the serum (Kikuchi *et al.*, 2008). Similar values were obtained in an earlier study (Rodvold *et al.*, 1997). Patients with infective exacerbations of chronic bronchiectasis were given a single 250 mg clarithromycin dose orally. Maximum sputum concentrations were 0.52 μg/ml of clarithromycin 5 hours after the dose and 0.3 μg/ml of the metabolite 6.5 hours after the dose (Tsang *et al.*, 1994). Clarithromycin suspension was given in a dosage of 7.5 mg/kg 12-hourly for 7 days to children with otitis media. The fifth dose was given 2.5 hours before aspiration of middle ear effusion. In the middle ear effusions, mean concentrations of clarithromycin (2.5 μg/ml) and metabolite (1.3 μg/ml) were higher than the serum concentrations (1.7 and 0.8 μg/ml, respectively) (Guay and Craft,

1993; Sundberg and Cederberg, 1994). The penetration of clarithromycin into the central nervous system is unknown. Although these various fluid concentrations of clarithromycin all technically exceed the minimum inhibitory concentrations of most common pathogens, the clinical relevance of such analyses has been questioned (Mouton *et al.*, 2008).

Clarithromycin has enhanced placental transfer compared with other macrolides (Witt *et al.*, 2003). Clarithromycin and its active metabolite, 14-hyrdoxy-clarithromycin, is distributed into breast milk (25% and 75%, respectively) with peak concentrations reached 2–3 hours post administration (Chung *et al.*, 2002). However, increased protein binding decreases the risk of absorption by infants during breastfeeding, and therefore is of little clinical importance (Chin *et al.*, 2001).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Similar to erythromycin (see Chapter 59, Erythromycin), clarithromycin is essentially bacteriostatic. The cure rate of macrolides mainly depends on the AUC/MIC ratio (Andes *et al.*, 2004), based on a time-dependent effect together with a postantibiotic effect, as shown both in *in vitro* and in animal models (Rolin and Bouanchaud, 1989; Novelli *et al.*, 2002).

A notable recent study suggested that the free AUC (0–24 hours) of clarithromycin (500 mg twice daily) was too low (0.39 and 0.41 mg/l h for subcutaneous tissue and skeletal muscle) to be effective in the treatment of soft-tissue infections caused by pathogens with a drug MIC higher than 0.125 mg/l (Traunmuller *et al.*, 2007).

5d. Excretion

Clarithromycin is metabolized in the liver and several metabolites are formed, but 14-hydroxy-clarithromycin (14-OH derivative) is the only microbiologically active metabolite, and it is also the only metabolite found in plasma in high concentrations. This metabolism is saturable, explaining why the pharmacokinetics of clarithromycin is not linear (Ferrero *et al.*, 1990). The main route of excretion of clarithromycin is in the urine, with only small amounts recovered in the bile or in the feces. Approximately 20–30% of an oral dose is excreted in urine as active clarithromycin and another 10–15% is recoverable in urine as the active metabolite (Chu *et al.*, 1992b; Rodvold and Piscitelli, 1993).

5e. Drug interactions

Drug interactions with macrolides are a considerable problem which seriously limit their use in at-risk patients. Thus, all patients receiving clarithromycin should undergo a review of potential drug interactions before prescribing the drug. The main clinically relevant interactions are summarized in Table 61.3.

The main mechanism involved in these interactions is the ability of macrolides to bind to cytochrome P450 (group 3A4 predominantly, but also 2C9, 2C19, and 1A2), thereby impairing the subsequent metabolization of other substrates of the same cytochrome (Periti *et al.*, 1992; Dresser *et al.*, 2000; Pai *et al.*, 2000; Pai *et al.*, 2006). The elimination of these co-administered drugs is therefore reduced, leading to a potential risk of toxicity (Periti *et al.*, 1992; von Rosensteil and Adam, 1995; Dresser *et al.*, 2000). This risk, however, is lower with clarithromycin than with erythromycin. As clarithromycin inhibits intestinal as well as hepatic cytochrome P450 isoenzymes, interaction potential is greatest with orally administered CYP3A4 substrates.

Potential life-threatening side-effects may be experienced when macrolides are co-administered with drugs liable to prolong the QT-interval and thereby increase the risk of torsades de pointes (van Haarst *et al.*, 1998; Curtis *et al.*, 2003). These include many anti-arrhythmics as well as several others (including cisapride, terfenadine, astemizole, and grepafloxacin, which were withdrawn from the market because of this adverse effect) (van Haarst *et al.*, 1998). The steady state concentration of loratadine does rise when given with clarithromycin, but no clinically significant QT-interval prolongation has been demonstrated (Carr *et al.*, 1998).

There have been several reports of interaction between clarithromycin and carbamazepine, with resulting increased serum carbamazepine levels (approximately doubled). Toxicity included drowsiness, dizziness, and ataxia (Richens *et al.*, 1990; O'Connor and Fris, 1994; Yasui *et al.*, 1997; Pauwels, 2002). Therefore, this combination should be avoided if possible and, if unable to do so, then carbamazepine dosage should be decreased by 25–50% and serum concentrations should be measured frequently (Pai *et al.*, 2000).

A 2- to 5-fold increase in serum concentrations of ciclosporin and tacrolimus can occur within a few days of starting clarithromycin, but start to normalize several days after stopping clarithromycin (Ferrari *et al.*, 1994; Gersema *et al.*, 1994; Sádaba *et al.*, 1998; Gómez *et al.*, 1999; Pai *et al.*, 2006). Therefore, increased therapeutic drug monitoring is necessary with concomitant use, to prevent potential nephrotoxicity. Similar drug interaction has been reported with the calcineurin inhibitors; tacrolimus (Wolter *et al.*, 1994; Katari *et al.*, 1997; Gómez *et al.*, 1999; Ibrahim *et al.*, 2002; Kunicki and Sobieszczańska-Małek, 2005), sirolimus (Capone *et al.*, 2007), and everolimus (Mignat, 1997).

HMG-CoA reductase inhibitors which are metabolized by cytochrome P3A4, such as atorvastatin, cerivastatin, lovastatin, and simvastatin, can also have a similar increase in their serum levels. This can result in myopathy and rhabdomyolysis, particularly in patients with renal insufficiency (Grunden and Fisher, 1997; Lee and Maddix, 2001; Amsden *et al.*, 2002; Jacobson, 2004; Molden and Andersson, 2007).

There are several interactions between clarithromycin and antiretroviral medications (Malaty and Kuper, 1999). These include protease inhibitors which inhibit CYP3A4 liver isoenzymes, including ritonovir, indinavir, saquinavir, amprenavir, and tipranavir. This interaction results in increased serum levels of both these protease inhibitors and clarithromycin. However, no dose adjustment is necessary if there is normal renal function (Ouellet *et al.*, 1998; Boruchoff *et al.*, 2000; Brophy *et al.*, 2000; Cvetkovic and Goa, 2003; la Porte *et al.*, 2009). Both nevirapine and efavirenz are CYP3A4 inducers and can decrease clarithromycin levels (Robinson *et al.*, 1999). Although, the nuclease reverse transcriptase inhibitors are not dependent on cytochrome P450 for elimination, effects on zidovudine pharmacokinetics has been described when zidovudine and clarithromycin are co-administered. A decrease in zidovudine C_{max} and AUC has been described (Polis *et al.*, 1997) but an increase in zidovudine's C_{max} has also been described (Vance *et al.*, 1995). It is unlikely that this interaction is clinically significant, although separation of administration of these two drugs by at least 2 hours is recommended (Petty *et al.*, 1997).

Another potentially significant interaction of clarithromycin is with midazolam (Yeates *et al.*, 1997; Gorski *et al.*, 1998). Pretreatment with clarithromycin significantly increased midazolam drug levels and increased drowsiness after a single dose (Yeates *et al.*, 1997).

Co-administration of omeprazole and clarithromycin increases omeprazole's serum levels (Calabresi *et al.*, 2004). This has also been described with esomeprazole and lansoprazole (Hassan-Alin *et al.*, 2006; Saito *et al.*, 2005). The serum peak level and AUC of clarithromycin and its concentrations in gastric mucus and tissue have also been noted to increase when given with omeprazole (Gustavson *et al.*, 1995) but not with esomeprazole (Hassan-Alin *et al.*, 2006).

Co-adminstration with ergotamine can lead to ergotism (Horowitz *et al.*, 1996; Ausband and Goodman, 2001). Newer antimigraine therapy such as sumatriptan has not shown this same interaction (Moore *et al.*, 2002). A fatal interaction between disulfiram and clarithromycin with resultant fatal toxic epidermal necrolysis and fulminant hepatic failure has been described (Masia *et al.*, 2002).

Table 61.3 Drug interactions with clarithromycin.

Drug class	Drug	Interaction	References
Antibiotics	Rifabutin, rifampicin	Decreased effect of macrolide. Increased effect and toxicity	Wallace *et al.*, 1995; Griffith *et al.*, 1996; Apseloff *et al.*, 1998; Hafner *et al.*, 1998; Jordan *et al.*, 2000; Baciewicz *et al.*, 2008
Antifungals	Itraconazole, Ketoconazole, Fluconazole	Increased effect and toxicity. Increased level of macrolide	
Antiretrovirals			
Protease inhibitors	Amprenavir, Atazanavir, Darunavir, Indivavir, Ritonovir, Saquinavir	Increased serum levels of both drugs	Ouellet *et al.*, 1998; Brophy *et al.*, 2000
NNRTI	Efavirenz, Nevirapine, Delavirdine	Decreased serum levels of macrolide. Increased levels of both drugs	Malaty and Kuper, 1999; Kuper and D'Aprile, 2000
NRTI	Zidovudine	Decreased serum levels	Polis *et al.*, 1997
Immunosuppressants			
	Ciclosporin	Increased effect of both drugs – nephrotoxicity	
Rapamycins	Everolimus, Tacrolimus, Sirolimus	Increased effect of both drugs – nephrotoxicity	Katari *et al.*, 1997; Capone *et al.*, 2007
Corticosteroids	Meythlprednisolone	Increased effect	Fost *et al.*, 1999
Cardiovascular agents			
	Digoxin	Increased effect of both drugs	
	Amiodarone, Bretylium, Dofetilide, Quinidine, Pimozide, Sotalol	Increased risk of arryhthmias	Desta *et al.*, 1999
	Disopyramide, Verapamil	Symptomatic hypotension	Kaeser *et al.*, 1998
Anticoagulants	Acenocoumarol, Anisindione, Dicoumarol, Warfarin	Increased effect of both drugs	Oberg, 1998
HMG coenzyme A reductase inhibitors ("Statins")	Atorvastatin, Cerivastatin, Lovastatin, Simvastatin	Increased toxicity. Rhabdomyolysis	Gruden and Fisher, 1997; Lee and Maddix, 2001; Amsden, *et al.*, 2002; Jacobson, 2004
	Eplerenone	Increased effect and toxicity	
	Ranolazine	Increased effect and toxicity	
Anticonvulsants			
Phenytoin	Fosphenytoin, Phenytoin	Increased effect and toxicity	
	Carbamazepine	Increased effect of both drugs	
Psychotropic drugs			
Benzodiazepines	Alprazolam, Diazepam, Midazolam, Triazolam	Increased effect of both drugs –excessive sedation	Quinney *et al.*, 2008
	Buspirone, Zopiclone	Increased effect and toxicity– excessive sedation	
	Citalopram, Fluoxetine, Sertraline	Possible serotoninergic syndrome	
	Quetiapine	Increased effect and toxicity. Arrhythmias	Schulz-Du Bois *et al.*, 2008
Antihistamines			
	Astemizole	Increased risk of cardiotoxicity and arryhthmias	
	Terfenadine	Increased risk of cardiotoxicity and arryhthmias	
Gastrointestinal			
	Cisapride	Increased risk of cardiotoxicity and arrhythmias	Sekkarie, 1997; Michalets and Williams, 2000
	Cimetidine	Increased serum levels of both drugs	Amsden *et al.*, 1998
Proton pump inhibitors	Omeprazole	Increased serum levels of both drugs	Calabresi *et al.*, 2004; 1995
	Esomeprazole	Increased serum levels of esomeprazole	Hassan-Alin *et al.*, 2004
	Lansoprazole	Increased serum levels of lansoprazole	Saito *et al.*, 2005
Hypoglycemic agents			
	Repaglinide	Increased effect	Khamaisi and Leitersdorf, 2008
	Sulfonylureas	Increased effect	Bussing and Gende, 2002
	Tolbutamide	Increased effect	Jayasagar *et al.*, 2000
Others			
	Colchicine	Increased toxicity	Dogukan *et al.*, 2001; Rollot *et al.*, 2004; Hung *et al.*, 2005; vander Veen *et al.*, 2008
Ergot derivatives	Dihydroergotamine Ergotamine, Methysergide	Possible ergotism	Ausband and Goodman, 2001
	Eletriptan	Increased effect and toxicity	
Dopamine D_2-receptor agonist	Carbegoline	Increased serum level	Nakatsuka *et al.*, 2006
Theophylline and derivatives	Aminophylline, Dyphylline, Theophylline, Oxtriphylline	Increased effect and toxicity	
Phosphodiesterase inhibitors	Sildenafil, Vardenafil	Increased effect and toxicity – symptomatic hypotension	
	Darifenacin	Increased serum levels of macrolide	
	Aprepitant	Increased effect and toxicity	
Aldehyde dehydrogenase inhibitor	Disulfiram	Increased effect and toxicity	Masia *et al.*, 2002

HMG: hydroxy methyl glutaryl; NRTI: nuclease reverse transcriptase inhibitor; NNRTI: non-nuclease reverse transcriptase inhibitor.

There have been cases of hypoglycemia in patients taking oral hypoglycemic drugs (Jayasagar *et al.*, 2000; Bussing and Gende, 2002; Khamaisi and Leitersdorf, 2008). Sulfonylureas are metabolized via the cytochrome P450 CYP2CP and CYP2C19 isoenzymes. This is also probably the basis of the interaction between clarithromycin and warfarin. There have been case reports of overanticoagulation occurring in patients receiving concomitant warfarin (Recker and Kier, 1997; Oberg, 1998). Patients on warfarin should have their prothrombin time/INR monitored closely while taking clarithromycin.

Conversely, co-administration of inducers of the cytochrome P450 3A4, such as rifampicin or rifabutin, cause a reduction of macrolide plasma levels, which can lead to therapeutic failure or selection of resistant strains because of the presence of sub-therapeutic clarithromycin concentrations. This effect is especially marked with rifampicin (Wallace *et al.*, 1995; Baciewicz *et al.*, 2008). Clarithromycin also acts via the cytochrome P450 system to increases rifabutin serum levels, and toxicities such as uveitis or neutropenia can occur (Griffith *et al.*, 1995; Apseloff *et al.*, 1998; Hafner *et al.*, 1998; Jordan *et al.*, 2000). In one study, risk of uveitis was reduced when rifabutin was reduced from 600 to 300 mg daily when given in combination with clarithromycin and ethambutol (Shafran *et al.*, 1998).

Clarithromycin is also known to be an inhibitor of P-glycoprotein (Kim, 2002). This may increase intestinal absorption or reduce renal elimination of drugs that are substrates for this transporter and possibly contribute to an increased risk of toxicity, especially when associated with inhibition of hepatic metabolism. Digoxin toxicity may be a result of this mechanism as digoxin is primarily renally cleared by P-glycoprotein-mediated tubular secretion. Administration of clarithromycin with digoxin results in increased oral bioavailability, decreased renal clearance, and increased serum digoxin concentrations (Rengelshausen *et al.*, 2003). This usually occurs within 4–7 days and is correlated with dose (Zapater *et al.*, 2002; Tanaka *et al.*, 2003). There have been numerous case reports of digoxin toxicity with the concomitant use of clarithromycin (Ford *et al.*, 1995; Midoneck and Etingin, 1995; Brown *et al.*, 1997; Guerriero *et al.*, 1997; Laberge and Martineau, 1997; Nawarskas *et al.*, 1997; Nordt *et al.*, 1998; Trivedi *et al.*, 1998; Gooderham *et al.*, 1999). Digoxin toxicity is particularly a problem in the elderly, with increased digoxin serum concentrations of ~70% described in elderly patients after 400 mg oral clarithromycin (Juurlink *et al.*, 2003; Tanaka *et al.*, 2003). Patients treated with both of these medications should have their renal function and digoxin levels monitored and adjustments made as necessary.

The potential interaction with colchicine is also probably via the mechanism of inhibition of P-glycoprotein (van der Veen *et al.*, 2008). A retrospective study of 116 patients found a 3-fold increased mortality with combination, compared with sequential therapy (10.2% *vs* 3.6%) (Hung *et al.*, 2005). Renal impairment was a particularly important underlying risk factor (Akdag *et al.*, 2006).

Clarithromycin, like the other macrolides, has minimal potential interaction with the oral contraceptive pill and has not been causally linked to pregnancy as a result of oral contraceptive failure (Arher and Archer, 2002).

6. TOXICITY

Overall, adverse effect rates of approximately 20% have been described in both adults and children (Guay *et al.*, 1993; Principi and Esposito, 1999; Block, 2006). Discontinuation rates secondary to side-effects have been 3–5% in most trials. Most adverse effects are mild to moderate and reversible with cessation of clarithromycin. Elderly patients may have increased rates of side-effects (Wallace *et al.*, 1993a).

Laboratory abnormalities have been noted in 0–1% of children and 3% of adults treated with clarithromycin (Guay *et al.*, 1993; Principi and Esposito, 1999). In these studies, liver function test abnormalities were the most common and all resolved after cessation of clarithromycin. Thrombocytopenia has also been uncommonly observed.

6a. Gastrointestinal adverse effects

Clarithromycin may cause some gastrointestinal disturbance; 3.8% nausea, 3% diarrhea, and 1.9% abdominal pain in adults in 3768 patients in phase II and III clinical trials (Guay *et al.*, 1993). Somewhat higher rates have been observed in children (7% diarrhea, vomiting 6%, nausea 1%, abdominal pain 2%) (Craft and Siepman, 1993). These side-effects are generally less than with erythromycin (17% *vs* 41%) (Guay *et al.*, 1993). However, Block *et al.* (1995), in a comparator study of clarithromycin with erythromycin, found similar rates of gastrointestinal side-effects (25% in both groups). Principi and Esposito (1999) reported 14–26% gastrointestinal side-effects in children with clarithromycin. These effects have been more frequently reported with the immediate-release than the extended-release form of clarithromycin. Taste alteration is also a frequently reported side-effect (~10–15%).

6b. Hepatotoxicity

Transaminase elevation of greater than three times the upper limits of normal occurs in 2–3% of patients. This is usually reversible upon completion of therapy (Abbott Laboratories, 2000). Several cases of fulminant acute hepatitis have been reported (Yew *et al.*, 1994; Shaheen and Grimm, 1996; Baylor and Williams, 1999; Christopher *et al.*, 2002; Tietz *et al.*, 2003). There is also a case report of fatal cholestatic liver disease after clarithromycin administration (Fox *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 human ether-a-go-go related gene channel-dependent potassium current in myocyte membranes (Roden, 2008). These interactions may give rise to polymorphic ventricular tachycardia, torsades de pointes, or ventricular fibrillation, as noted by Hensey and Keane (2008) for clarithromycin. In a rat model, the potency of macrolides to induce QTc prolongation was ranked as follows: erythromycin > clarithromycin > roxithromycin > azithromycin (Ohtani *et al.*, 2000). In a small group of 28 children, a mean QTc prolongation of 22 ms was observed but, in seven children, a QTc greater than 440 ms was observed (Germanakis *et al.*, 2006). In a small group of adults, the mean increase was 11 ms only (Carr *et al.*, 1998). Of 156 cases of torsades de pointes associated with macrolide use, reported to the USA Food and Drug Administration Adverse Event Reporting System from 1987 to 2000, 36% were attributed to clarithromycin. It should be noted that half of these patients were also receiving another medication, which is associated with QT prolongation such as cisapride (Shaffer *et al.*, 2002). Predisposing factors were female gender, pre-existing heart disease, electrolyte disturbances, reduced drug elimination because of drug interactions or renal or hepatic dysfunction, and concomitant QT interval prolonging medications such as cisapride (van Haarst *et al.*, 1998; Piquette, 1999; Iannini 2002; Shaffer *et al.*, 2002; Simkó *et al.*, 2008). Therefore, in patients with other multiple risk factors, clarithromycin should be avoided.

6d. Hypersensitivity reactions

Allergic reactions including eosinophilia, fever, and skin eruptions are rarely reported for macrolides (Periti *et al.*, 1993; Hamamoto *et al.*,

2001), and they usually disappear upon cessation of treatment. There may be cross-reactivity to different macrolides as positive skin prick testing has been reported with roxithromycin, erythromycin, and clarithromycin (Kruppa *et al.*, 1998). There has been a case report of immediate hypersensitivity with bronchospasm (Gangemi *et al.*, 2001). Toxic reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis have been reported very rarely (Masia *et al.*, 2002; Baz *et al.*, 2004). A few cases of leukocytoclastic vasculitis and Henoch–Schönlein purpura have been associated with the use of clarithromycin (de Vega *et al.*, 1993; Gavura and Nusinowitz, 1998; Goldberg *et al.*, 1999; Borrás-Blasco *et al.*, 2003).

6e. Hematologic toxicity

Leukopenia (white blood cell count $<2 \times 10^9$/l) or thrombocytopenia (platelet count $<75 \times 10^9$/l) develop in 2–3% (Price and Tuazon, 1992; Abbott Australasia product information, 2008). Agranulocytosis has been described with the use of clarithromycin (Jacobs *et al.*, 2004). There have also been some case reports of thrombocytopenic purpura developing in patients taking clarithromycin (Oteo *et al*, 1994; Alexopoulou *et al.*, 2002).

6f. Neurotoxicity

Headache occurs in ~2% adults and children (Craft, 1993; Guay *et al.*, 1993). Clarithromycin has been associated with transient cases of neurologic effects such as anxiety, confusion, insomnia, psychosis, tremor, dizziness, vertigo, convulsions, and disorientation (Abbott Laboratories, 2000; Prime and French, 2001). These are reversible with discontinuation of the drug. Psychiatric effects such as hallucinations and mania have also been reported (Steinman and Steinman, 1996; Jiménez-Pulido *et al.*, 2002; Kouvelou *et al.*, 2008). The reason for this has not been fully elucidated, but macrolides may inhibit glutamatergic neurotransmission (Manev and Favaron, 1993).

6g. Ototoxicity

A study in guinea-pigs showed a single high intravenous dose of clarithromycin (75 mg/kg) reversibily reduced transiently evoked otoacoustic emissions (Uzun *et al.*, 2001). In phase I trials, 184 healthy volunteers had audiologic testing; minor, not clinically significant, alterations were detected in 9%. In phase II and III trials, two patients with AIDS and *M. avium* complex infection, treated with prolonged high doses of 1000 mg twice daily for 6 weeks, had partial hearing loss (Guay *et al.*, 1993). However, there have been few case reports of this adverse effect since then, although it may be an underrecognized problem.

6h. Risk in pregnancy

Clarithromycin is FDA pregnancy category C and should be avoided during pregnancy. Animal studies have found an increased rate of cardiovascular abnormalities, cleft palate, and embryonic loss with high doses (Guay *et al.*, 1993). A North American retrospective study of 143 women who were exposed to clarithromycin during the first trimester did not identify as statistically significant differences in major or minor malformations compared with national rates (3.4% *vs* 2.8%) (Drinkard *et al.*, 2000). Einarson *et al.* (1998) performed a prospective case–control study of 157 pregnant women who were exposed to clarithromycin. Most (122 women) had received the drug during the first trimester. They were matched with other pregnant women who had received other antibiotics. There was no significant differences between the two groups for major malformations (2.3% *vs* 1.4%) or minor malformation (5.4% *vs* 4.9%). However, spontaneous abortion rates were significantly higher (14% *vs* 7%; $p = 0.04$) in the clarithromycin group. Like erythromycin, clarithromycin has been shown to dose dependently inhibit human myometrium in *in vitro* studies (Celik and Ayar, 2002).

7. CLINICAL USES OF THE DRUG

Clarithromycin is approved for the treatment of acute streptococcal pharyngitis, acute otitis media, acute sinusitis, acute bacterial exacerbations of chronic bronchitis, community acquired pneumonia, disseminated or localized mycobacterial infections, skin infections, prevention of disseminated *M. avium* complex infection in HIV infected adults, and peptic ulcer disease in combined therapy. Other clinical indications for clarithromycin include Chlamydial infections, leprosy, Q fever, and Lyme disease. There is some evidence for its role as an immunomodulatory agent, particularly in respiratory disease. A comparison of the clinical use of clarithromycin compared with other macrolides is summarized in Table 61.4.

Macrolides have long been considered as an alternative to beta-lactams for the treatment of respiratory tract infections. The immediate-release and extended-release formulations of clarithromycin are approved for the treatment of community-acquired respiratory infections, with success rates similar to those of beta-lactams in some

Table 61.4 Potential clinical indications for various macrolides in settings where macrolide susceptibility is likely.

Organism or disease	Erythromycin	Clarithromycin	Azithromycin
Otitis media	Yes	Yes	Yes
Pharyngitis	Yes	Yes	Yes
Sinusitis	Yes	Yes	Yes
Acute infective exacerbation of chronic bronchitis	Yes	Yes	Yes
Community-acquired pneumonia	Yes	Yes	Yes
Legionella spp.	No	Yes (outpatient)	Yes
Helicobacter pylori	No	Yes	Investigational
Chlamydia trachomatis	Yes	No	Yes
Lymphogranuloma venereum	Yes	No	Promising
Campylobacter	Yes	Yes	Yes
MAC treatment	No	Yes[a]	May be alternative[a]
MAC prophylaxis	No	Yes	Yes
Mycobacterium chelonae	No	Yes	No
Mycobacterium abscessus	No	Yes	
Mycobacterium leprae	No	Yes	No

Adapted from Blondeau *et al.* (2002).
[a]Use in combination with at least one other MAC-active antibiotic. MAC: *Mycobacterium avium* complex.

studies (Darkes and Perry, 2003). However, the increasing rate of resistance among many respiratory pathogens to macrolides (in particular *S. pneumoniae* and *S. pyogenes*) 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). Macrolide resistance among 3778 *S. pneumoniae* isolates from multiple centers in numerous countries from 1997 to 2000, was highest in Asia (51.7%), with rates variable elsewhere: 26% in Europe, 21.6% in North America, 13.7% in the Middle East, 10.6% in the South Pacific, and 10.0% in Africa (Bouchillon *et al.*, 2004).

7a. Upper respiratory tract infection

Pharyngitis

In pharyngitis, claritromycin has been shown to be as effective as penicillin V or amoxicillin–clavulanate, but should be used only in areas where macrolide resistance among *S. pyogenes* isolates is low (Portier *et al.*, 2002; Syrogiannopoulos *et al.*, 2004). The dosage recommended for this indication is 250 mg twice-daily immediate-release preparation or 500 mg extended-release preparation (7.5 mg/kg twice-daily in children) for 5–10 days. Large randomized controlled trials have shown clinical cure rates of 81–94% (McCarty *et al.*, 2000; Quinn *et al.*, 2003; Takker *et al.*, 2003; Kafetzis *et al.*, 2004) and bacterial eradication rates of between 83% and 94% (Venuta *et al.*, 1998; Quinn *et al.*, 2003; Takker *et al.*, 2003; Kafetzis *et al.*, 2004; Syrogiannopoulos *et al.*, 2004). Clarithromycin appears to be as effective as phenoxymethylpenicillin in the eradication of streptococci from the nasopharynx. However, penicillin remains the usual drug of choice in the treatment and prevention of streptococcal infections. Substantial data establishing the efficacy of clarithromycin in preventing the development of rheumatic fever is not available at present.

Sinusitis

Clarithromycin 500 mg twice daily for adults or 7.5 mg/kg twice daily for children, or 1000 mg of extended-release formulation for 7–14 days, is indicated in the treatment of sinusitis (Murray *et al.*, 2000; Rechtweg *et al.*, 2004; Riffer *et al.*, 2005). Clarithromycin has been shown to reduce mucus secretion in those with purulent rhinitis as well as normal subjects (Rubin *et al.*, 1997). Clinical cures of 79–94% and radiologic cures of 90–96% have been shown in clinical trials (Adelgalss *et al.*, 1998; Riffer *et al.*, 2005). This is similar to amoxicillin–clavulanic acid. Similar clinical cure rates were seen in a study comparing immediate-release and extended-release formulations (Murray *et al.*, 2000).

Otitis media

Clarithromycin has also been shown to be useful in the treatment of otitis media (Aspin *et al.*, 1994; Pavlopoulou *et al.*, 1995; Arguedas *et al.*, 1997; Block 1997; Quach *et al.*, 2005). It has previously been shown to have similar efficacy to beta-lactam therapy for acute otitis media with effusion in children (Arguedas *et al.*, 1997). As there is increasing macrolide resistance in *S. pneumoniae*, this now limits its usefulness. In addition, the overall need for any antibiotics in otitis media has been questioned since the condition is so frequently as a result of viral causes.

7b. Lower respiratory tract infection

Acute bacterial exacerbations of bronchitis/chronic obstructive airways disease

Both immediate-release and extended-release clarithromycin of 5–10 days has been shown to be effective in treatment of acute bacterial exacerbations of bronchits/chronic obstructive airways disease, with clinical cure rates of 78–98% (Anzueto *et al.*, 1997; Anzueto *et al.*, 1998; Chodosh *et al.*, 1998; Ziering and Mcelvaine, 1998; Adler *et al.*, 2000; Adam *et al.*, 2001; Anzueto *et al.*, 2001; Gotfried *et al.*, 2001; Weiss, 2002; Weiss *et al.*, 2002; Wilson *et al.*, 2002; Nalepa *et al.*, 2003; Fogarty *et al.*, 2005; Gotfried *et al.*, 2005; Gotfried *et al.*, 2007). However, the same issues of emerging resistance as described above, are also likely to affect its clinical use in this area.

Community-acquired pneumonia

Clarithromycin's main role in the treatment of pneumonia is for the treatment of atypical respiratory infections caused by intracellular pathogens such as *M. pneumoniae* and *C. pneumoniae* (Block *et al.*, 1995; Numazaki *et al.*, 2000; Bonvehi *et al.*, 2003; Roig *et al.*, 2006; Lee *et al.*, 2008). Doses used are similar: 500 mg orally twice daily for the immediate-release formulation and 1000 mg orally daily for the extended-release formulation (Allin *et al.*, 2001). Duration of therapy is usually 7–10 days.

Clarithromycin has been shown to have similar efficacy to other antibiotics in the treatment of community-acquired pneumonia. This includes other macrolides such as azithomycin (Sopena *et al.*, 2004), telithromycin (Mathers Dunbar *et al.*, 2004; Niederman *et al.*, 2004; Tellier *et al.*, 2004), roxithromycin (Tatsis *et al.*, 1998), beta-lactams (Genné *et al.*, 1997; Langtry and Brogden, 1997; Bonvehi *et al.*, 2003), gatifloxacin (Dean *et al.*, 1999; Lode *et al.*, 2004; Dean *et al.*, 2006), trovafloxacin (Sokol *et al.*, 2002), and moxifloxacin (Hoeffken *et al.*, 2001). Most of these studies have been conducted in nonhospitalized patients. A study of dual therapy with clarithromycin and cefuroxime versus clarithromycin alone for treatment of outpatient community pneumonia did not show any additional benefits (Rovira *et al.*, 1999). Clarithromycin has increased side-effects, particularly gastrointestinal, compared with azithromycin, and hence azithromycin is often preferred (Sopena *et al.*, 2004; Tamm *et al.*, 2007).

Macrolide resistance is an increasing problem in *S. pneumoniae*. There have been several studies showing clinical failure with resistant isolates of *S. pneumoniae* during clarithromycin therapy (Kelley *et al.*, 2000; Lonks *et al.*, 2002; Kelley *et al.*, 2003; Schentag *et al.*, 2007). In one study, the mean AUC/MIC was much lower in those patients with failure (Schentag *et al.*, 2007). For this reason, clarithromycin and other macrolides are proposed as first-line therapy of community-acquired pneumonia only 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). Similar to azithromycin (see Chapter 62, Azithromycin), a combination of clarithromycin with amoxicillin (-clavulanate) is recommended in countries with high rates of macrolide-resistant pneumococci when treatment for "atypical" pathogens is suitable (García Vázquez *et al.*, 2005; Mandell *et al.*, 2007; Tamm *et al.*, 2007).

Legionella pneumonia

Clarithromycin is also active against *L. pneumophila* at a dose of 500–100 mg twice daily for 10–21 days (Hamedani *et al.*, 1991; Roig *et al.*, 1993; Amsden, 2005; Roig *et al.*, 2006). If hospitalization is required, parenteral azithromycin should be given if available, or another suitable macrolide (Amsden, 2005). It has been suggested that fluoroquinolones may produce a better response (Pedro-Botet and Yu, 2006). A combination with rifampicin has also been used.

Pertussis

Clarithromycin is one of the three macrolides recommended for treatment and post-exposure prophylaxis of pertussis (Tiwari *et al.*, 2005; Antibiotic Expert Group, 2006; Altunaiji *et al.*, 2007).

Clarithromycin is not recommended for infants less than one month of age, as safety data are unavailable. In particular, it is unknown if, like erythromycin, it is associated with infantile hypertrophic pyloric stenosis. The recommended pediatric dosage is 7.5 mg/kg twice daily (maximum 1 g daily) and the adult dosage is 500 mg twice daily for a duration of 7 days. Microbiologic eradication was achieved in 100% cases with 10 mg/kg daily (maximum 400 mg) for 7 days of clarithromycin in nine children (Aoyama *et al.*, 1996). None relapsed at 2 weeks. A larger study in 76 children in Canada had similar results with 7.5 mg/kg twice daily for 7 days (Lebel and Mehra, 2001). This is better than erythromycin (80–96%) and similar to azithromycin (Tiwari *et al.*, 2005).

7c. Skin infections

Clarithromycin can be used for non-complicated skin and skin-structure infections caused by susceptible *S. aureus* or *S. pyogenes*, although penicillins are preferred. It has similar clinical efficacy to erythromycin (Northcutt *et al.*, 1990). Early studies of clarithromycin 250 mg twice daily compared favorably with cefadroxil 500 mg twice daily; 89% *vs* 92% organism eradication and 77% and 79% clinical cure rates, respectively (Clarithromycin Study Group, 1993). However, both *S. aureus* and Group A Streptococcus can display high rates of macrolide resistance, and hence clarithromycin is no longer recommended for this use (Cornaglia *et al.*, 1998; Nakaminan *et al.*, 2008).

7d. *Helicobacter pylori*-associated gastritis and peptic ulcer disease

Clarithromycin 500 mg twice daily for 14 days, in combination with 1 g amoxicillin (or metronidazole 500 mg twice daily) and omeprazole or lansoprazole is the first-line treatment of *H. pylori* gastritis (Dzieniszewski and Jarosz, 2006; Malfertheiner *et al.*, 2007). Omeprazole increases the concentration of clarithromycin in gastric tissue and mucus, and this may be one of the explanations for the success of this regimen (Gustavson *et al.*, 1995). However, resistance to clarithromycin is increasing all over the world and this will significantly impact the choice of therapy in the near future (Bruce *et al.*, 2006; Kumala and Rani, 2006; Chisholm *et al.*, 2007; Kobayashi *et al.*, 2007; Boyanova *et al.*, 2008; Liu *et al.*, 2008; Tuzun *et al.*, 2008). Clarithromycin resistance is a key factor for treatment failure of *H. pylori* disease (Pilotto *et al.*, 1999; McMahon *et al.*, 2003). The prevalence of *H. pylori* resistance to clarithromycin varies from 5% to 20% in many parts of Europe, Asia, and the USA (Duck *et al.*, 2004; Lee *et al.*, 2005; Koletzko *et al.*, 2006; Kulsuntiwong *et al.*, 2008; Boyanova *et al.*, 2009; Hung *et al.*, 2009; Megraud, 2009; Woo *et al.*, 2009; Wueppenhorst *et al.*, 2009). Resistance is related to previous use of macrolides (Cars *et al.*, 2001). Rates are often higher in children because of the increased use of macrolides to treat respiratory infections in this group (Koletzko *et al.*, 2006). Strains with the A2143G mutations appear to be associated with a very low eradication rate with standard triple therapy (Taylor, 2000; De Francesco *et al.*, 2006; see above under 2b. Emerging resistance and cross-resistance). It is recommended that clarithromycin should not be used or clarithromycin susceptibility testing should be performed if there are resistance rates of 15–20% in a population (Malfertheiner *et al.*, 2007).

A recent meta-analysis of *H. pylori* therapy revealed that standard triple therapy resulted in *H. pylori* eradication in 71% ($n = 1384$; 95% CI 64–77%) (Jafri *et al.*, 2008). This was somewhat lower than an earlier meta-analysis which focused on European data in which eradication rates were 80.5% (95% CI 77.2–84.2%) (Buzás and Józan, 2006).

The usual duration of therapy is 7 days. One meta-analysis showed a higher eradication rate (12%; 95% CI 7–17%) with 14 days of therapy, and it has been suggested that this should be adopted as standard practice (Ford and Moayyedi, 2003). However, this finding has not been confirmed in subsequent studies (De Francesco *et al.*, 2004; Zagari *et al.*, 2007).

7e. *Mycobacterium avium* complex infections

Disseminated *Mycobacterium avium* complex in HIV

Clarithromycin and azithromycin (see Chapter 62, Azithromycin) are now key drugs for the treatment of disseminated MAC infection (Shafran *et al.*, 1996; Ward *et al.*, 1998). Macrolides should not be used as single agents as resistance among *M. avium* strains develops readily (Chaisson *et al.*, 1994). Ethambutol (± rifampicin) are used in first-line combinations (Benson, 1994; Gordin *et al.*, 1999; Griffith *et al.*, 2007); amikacin or moxifloxacin are considered only in cases of resistance (Griffith *et al.*, 2007). In a prospective randomized trial, clarithromycin combined with both ethambutol and rifampicin proved more effective in terms of bacterial eradication and prevention of relapse than when combined with only one of these antibiotics (Benson *et al.*, 2003). The maximum dose of clarithromycin for this indication is 500 mg twice daily. Higher doses having been associated with increased mortality (Cohn *et al.*, 1999). Therapy can be discontinued with resolution of symptoms and reconstitution of cell-mediated immune function.

Mycobacterium avium complex prophylaxis in patients with HIV

Clarithromycin (500 mg twice daily) is also effective in the prophylaxis of MAC infections (Pierce *et al.*, 1996) in patients with fewer than 50 $CD4^+$ T-cells/μl (Kaplan *et al.*, 2002). However, azithromycin is preferred because of its easier therapeutic scheme (1200 mg once weekly), which favors compliance and decreases therefore the risk for selection of resistance (Oldfield, III *et al.*, 1998). Prophylaxis is indicated until $CD4^+$ T-lymphocyte counts are > 100 cells/μl for more than three months (Masur *et al.*, 2002).

Mycobacterium avium complex pulmonary infection in patients without HIV

Clarithromycin and ethambutol are the cornerstones in the treatment of MAC lung disease, and are often combined with rifampicin (Dautzenberg *et al.*, 1995; Field *et al.*, 2005; Griffith *et al.*, 2006). The regimen for patients with severe and extensive diseases consists of 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). This is often not well tolerated, especially in the elderly (Wallace *et al.*, 2003). Drop-out rates in clinical trials have been about 20% (Field *et al.*, 2004). If the patient is elderly or weighs <50 kg, dosage reduction of clarithromycin to 500 mg/day or 250 mg twice daily may be necessary because of gastrointestinal intolerance.

There is variability between studies in the reported success rates of this therapy. Wallace's initial study of a regimen containing clarithromycin 500 mg twice daily also included ethambutol, rifampicin or rifabutin, and initial streptomycin. Therapy was continued until sputum culture was negative for 12 months. More than 20% of patients withdrew within the first three months, and, in intention-to-treat analysis, 54% (32/59) had successful therapy (Wallace *et al.*, 1996). Of those patients who completed at least three months of therapy, 82% (32/39) remained sputum culture negative after therapy cessation. Tanaka *et al.* (1999) noted similar findings with a regimen containing clarithromycin 10 mg/kg/day plus ethambutol, rifampicin, and initial kanamycin and subsequent quinolone for 24 months. Study drop-out was 15% before six months, and 61% (28/46) had successful

therapy on intention-to-treat analysis. Of those who were able to complete more than six months of therapy, 71.8% (28/39) had sputum conversion. A study using lower dose clarithromycin of 400–600 mg daily in a regimen that included ethambutol, rifampicin, and initial streptomycin for 12 months showed a much smaller benefit (Kobashi and Matsushima, 2003). Only 25/71 (35%) had long-term sputum clearance. A more recent study of a 24-month regimen containining ethambutol, rifampicin, and clarithromycin 500 mg twice daily showed clearance of sputum at 24 and 30 months of all 12 patients with MAC who completed therapy (two required clarithromycin substituted by ciprofloxacin because of nausea, but they also had sputum clearance) (Murray *et al.*, 2008).

For those patients who cannot tolerate higher dose clarithromycin and also those with less severe disease, intermittent, three-times-weekly therapy is an alternative (Griffith *et al.*, 2000). This includes (1) clarithromycin 1000 mg, (2) ethambutol 25 mg/kg, and (3) rifampicin 600 mg given three times weekly (Griffith *et al.*, 2007). Conversion to sputum culture negativity was 78% (32/41) in one study of this regimen at six months, although this was interim data (Griffith *et al.*, 2000). In one study, participants in an inhaled interferon-γ trial for MAC were treated with either clarithromycin or azithromycin, ethambutol and rifampicin, or rifambutin. Those with cavitary disease, a history of chronic obstructive pulmonary disease or bronchiectasis and previous treatment for pulmonary MAC did less well on this regimen (Lam *et al.*, 2006).

Clarithromycin has been used to treat MAC and other mycobacterial infections in children with cystitic fibrosis. However, data are limited.

Routine susceptibility testing of clarithromycin for MAC should be performed (Kobashi *et al.*, 2006; Griffith *et al.*, 2007). This should occur before commencement of therapy and on any isolates when there is failure of MAC treatment or prophylaxis. Untreated MAC isolates usually have MICs of 4 mg/l or less. Relapse strains commonly have a clarithromycin MIC of 32 mg/l or more (Heifets *et al.*, 1993). All high-level clarithromycin-resistant isolates have a single mutation in the 23S rRNA gene at the presumed macrolide binding site on the ribosomal unit (Meier *et al.*, 1996). This mutation results in cross-resistance between clarithromycin and azithromycin.

7f. Other atypical Mycobacterial infections

Macrolides, especially clarithromycin, in combination with other agents, is recommended for the treatment of non-tuberculous mycobacterial skin and soft-tissue infections (Stevens *et al.*, 2005). Therapy should be prolonged therapy (6–12 weeks or more).

Mycobacterium kansasii exhibits *in vitro* sensitivity to clarithromycin. One study of the combination regimen of three times weekly clarithromycin 500–1000 mg, rifampicin (600 mg), and ethambutol in those with pulmonary disease resulted in successful treatment of all 15 participants with a four-year follow-up (Griffith *et al.*, 2003). However, there is more evidence for rifampicin, isoniazid, and ethambutol combination therapy in this disease. Clarithromycin may have a role in rifampicin-resistant disease.

Although, there are no proven drug regimens for *M. abscessus* pulmonary disease, clarithromycin (1000 mg daily) containing combinations may be associated with symptomatic improvement and disease regression (Griffith *et al.*, 2007). However, clarithromycin resistance can develop. Treatment of nonpulmonary disease caused by *M. abscessus* also frequently involves macrolide therapy with clarithromycin or azithromycin in combination with parenteral amikacin, cefoxitin, or imipenem.

Mycobacterium chelonae is usually sensitive to clarithromycin (Brown *et al.*, 1992). A trial of clarithromycin monotherapy (500 mg bid for at least four months) for skin disease, predominantly as a manifestation of disseminated disease, resulted in successful treatment of 11/14 (two died during the study and one ceased therapy and then developed a clarithromycin-resistant recurrence) (Wallace *et al.*, 1993b). A multi-drug clarithromycin-containing regimen is recommended for serious skin and soft-tissue infection and osteomyelitis (four and six months, respectively). Optimal therapy for pulmonary disease is not known, but a clarithromycin-containing regimen is likely to be successful. Oral or topical (solution of 10–40 mg/ml) clarithromycin can also be used for corneal infections, although local discomfort can occur with the topical preparation (Ford *et al.*, 1998).

Mycobacterium fortuitum isolates are usually sensitive to clarithromycin on *in vitro* testing, but they often contain the inducible macrolide resistance gene (erythromycin methylase *erm*), and therefore macrolides should be used with caution (Brown *et al.*, 1992; Nash *et al.*, 2005).

The slow grower *M. marinum* is usually susceptible to clarithromycin. In one study, clarithromycin, given mainly in combination with rifampicin and/or ethambutol, resulted in resolution of skin and soft-tissue infections in 92% (22/24) cases. For those with deeper infection such as osteomyelitis there was resolution in 67% (10/15) cases (Aubry *et al.*, 2002). Griffith *et al.* (2007) recommend therapy with a combination of clarithromycin and ethambutol, with the addition of rifampicin if osteomyelitis is present.

There are limited data available regarding the use of clarithromycin in treatment of Buruli ulcer (caused by *M. ulcerans*), although a case of successful treatment with 8 weeks of clarithromycin and rifampicin in a pregnant woman has been published (Dossou *et al.*, 2008). Rifampicin and streptomycin is the current WHO-approved treatment regimen.

7g. Leprosy

Clarithromycin appears rapidly bactericidal for *M. leprae* in humans. In one clinical trial, clarithromycin was given to nine previously untreated patients with leprosy (Chan *et al.*, 1994). Patients received two 1500 mg doses on the first day, followed by 7 days of no treatment, in order to evaluate the efficacy of intermittent therapy. Thereafter, they received 1000 mg daily for 2 weeks followed by 500 mg daily for 9 weeks. Within 3 weeks, biopsy-derived *M. leprae* specimens were noninfectious for mice, and significant clinical improvement was evident after 4 weeks of treatment. Clarithromycin 500 mg and rifampicin 600 mg daily was also given successfully to another eight patients with both borderline lepromatous and lepromatous disease. In this study, severeal different regimens were compared and results were similar to those treated with long-term daily dapsone 100 mg and rifampicin 600 mg, and daily minocycline 100 mg and rifampicin 600 mg (Rea, 2000). However, the exact role of clarithromycin for this indication remains unclear. The current WHO recommendation for multibacilary leprosy treatment is clofazimine 50 mg daily and dapsone 100 mg daily, and once-monthly rifampicin 600 mg, clofazimine 300 mg and dapsone 100 mg for 12–18 months. A regimen containing daily clarithromycin 500 mg, rifampicin 600 mg, sparfloxacin 200 mg, and minocycline 100 mg for just 12 weeks compared favorably with the longer WHO regimen (Tejasvi *et al.*, 2006). In this randomized controlled trial of 30 patients, the net percentage reduction in morphologic index in both groups was 100% by 8 weeks. The net percentage reduction in bacterial index was also similar in both groups at 48 weeks (18.87% *vs* 19.17%; $p = 0.09$).

7h. Genitourinary infection

Unlike azithromycin, clarithromycin is not generally recommended in standard guidelines for treatment of genitourinary infections, including non-gonococcal urethritis, caused by *C. trachomatis*, *U. urealyticum*, and *M. genitalium*, *H. ducreyi*, and *K. granulomatis* infections (Centers for Disease Control and Prevention, 2006). Although, clarithromycin is potentially effective, azithromycin or doxycycline are the preferred antimicrobials. Azithromycin's prolonged half-life offers a distinct

clinical advantage compared with the need for twice-daily dosing for up to 14 days for clarithromycin (Skerk *et al.*, 2002; Mikamo *et al.*, 2003).

7i. Other infectious diseases

Chlamydia eye infections

Clarithromycin has been used successfully to treat neonatal conjunctivitis due to both C. *pneumoniae* and C. *trachomatis* (Krasny *et al.*, 2005). Dosing was 15 mg/kg/day for 14 days.

Toxoplasmosis

In one uncontrolled clinical trial, clarithromycin 2 g daily plus pyrimethamine 75 mg daily for 6 weeks appeared about equally effective to the conventional therapy of sulfadiazine plus pyrimethamine for therapy of acute toxoplasma encephalitis in patients with AIDS (Fernandez-Martin *et al.*, 1991). Combination therapy with minocycline has also been described (Lacassin *et al.*, 1995). However, breakthrough toxoplasmosis has been described in patients already taking clarithromycin (Raffi *et al.*, 1995). The role for clarithromycin for this indication still remains uncertain. Clarithromycin is not recommended for toxoplasma prophylaxis (Masur *et al.*, 2002).

Lyme disease

Macrolide antibiotics are less effective than other antimicrobials for the treatment of Lyme disease, despite being highly active *in vitro* against *B. burgdorferi* (Hunfeld *et al.*, 2004). However, in patients who are unable to tolerate amoxicillin, doxycycline, or cefuroxime (pregnant women and children with β-lactam allergy), clarithromycin 500 mg twice daily for 14–21 days may be an alternative (Dattwyler *et al.*, 1996; Wormser *et al.*, 2006). These patients need to be monitored closely for clinical resolution. The addition of hydroxychloroquine to clarithromycin may improve clinical response (Donta, 2003).

Q fever

Q fever (*C. burnetii*) has been successfully treated with clarithromycin (Gikas *et al.*, 2001; Jover-Díaz *et al.*, 2001; Morovic, 2005). Macrolides appear more effective than beta-lactams, although doxycycline remains the standard first-line agent. Clarithromycin has been proposed as an alternative for pregnant women (Ko *et al.*, 1997) but there are safety concerns and erythromycin is preferred. Gikas *et al.*, (2001) reported 15 cases of Q fever treated with clarithromycin. Fever took longer to resolve than for those patients who received doxycycline (4 *vs* 9 days; $p<0.05$). However, similar time to resolution of fever with doxycycline, moxifloxacin, and clarithromycin were seen in a larger study (2.4, 2.2, and 1.9 days, respectively) (Morovic, 2005).

Mediterranean spotted fever

Macrolides have *in vitro* activity against many rickettsial organisms (Rolain *et al.*, 1998). Their main role is in the treatment of children and pregnant women for whom tetracyclines and chloramphenicol have many potential serious adverse effects. Both clarithromycin and azithromycin were shown to be equally efficacious in the one study in the treatment of *R. conorii* infection in children (Cascio *et al.*, 2002). Eighty-seven children were randomized to receive either clarithromycin 7.5 mg/kg twice daily for 7 days or aizthromycin 10 mg/kg daily for 3 days. All had fever defervescence within 7 days, and there was no significant difference between the groups in terms of efficacy or tolerability. However, azithromycin's simpler, shorter course offers a distinct advantage.

Anthrax

Clarithromycin has *in vitro* activity against *B. anthracis*. It is one of the secondary antimicrobials that could be added to doxycycline or ciprofloxacin for treatment of inhalational anthrax (Brook, 2002).

7j. Immunomodulatory effects and uses

Respiratory disease

It has been suggested that the immunomodulatory properties of clarithromycin may play a role in the treatment of sinusitis (Gotfried, 2004; MacLeod *et al.*, 2001), asthma, (Hasegawa *et al.*, 2000; Richeldi *et al.*, 2005), chronic obstructive pulmonary disease (COPD, Bishai, 2006), cystic fibrosis (Pukhalsky *et al.*, 2004), and diffuse panbronchiolitis (Keicho and Kudoh, 2002; Kadota *et al.*, 2003). However, many of the studies in these areas have focused on azithromycin (see Chapter 62, Azithromycin). Macrolides increase mucociliary clearance and decrease mucosal inflammation, nasal secretions, and polyp size in patients with sinusitis (MacLeod *et al.*, 2001; Gotfried, 2004).

Clarithromycin has been shown to reduce IL-8 and neutrophil activity *in vitro* and has been shown to do the same in those with refractory asthma (Simpson *et al.*, 2008). There have been conflicting reports of improvement in pulmonary function and airway hyperresponsiveness (Amayasu *et al.*, 2000; Kostadima *et al.*, 2004; Simpson *et al.*, 2008). However, atypical intracellular pathogens may play a role in the pathogenesis of reactive airway diseases. One study in stable asthmatics treated with clarithromycin showed an improvement in pulmonary function tests in only those with positive PCR for M. *pneumoniae* and C. *pneumoniae* (Kraft *et al.*, 2002). Data demonstrating benefit in COPD are also not consistent (Garey *et al.*, 2000; Tagaya *et al.*, 2002; Banerjee *et al.*, 2004; Basyigit *et al.*, 2004; Banerjee *et al.*, 2005).

Retrospective analyses of patients treated for community-acquired pneumonia suggest that those treated with a combination of a beta-lactam and a macrolide may have reduced mortality compared with those treated with beta-lactam monotherapy (Martínez *et al.*, 2003; García Vázquez *et al.*, 2005; Metersky *et al.*, 2007). Subsequently, clarithromycin has been studied as an immunomodulatory agent in patients with nosocomial Gram-negative ventilator-associated pneumonia (Giamarellos-Bourboulis, 2008). Two hundred patients were randomized to either 1 g of clarithromycin for 3 days or placebo. Those who received clarithromycin were less likely to die from septic shock and multi-organ dysfunction (OR 3.78 *vs* 19.00; $p = 0.043$). However, overall mortality data were not presented.

In many patients with chronic lung disease, infection or colonization with mucoid strains of *P. aeruginosa* occur. They hyperproduce algination and exist as a biofilm. Macrolides, including clarithromycin, have also been shown to inhibit biofilm formation (Yasuda *et al.*, 1993; Bui *et al.*, 2000). One of the mechanisms for this may be their inhibition of pseudomonal cell-to-cell signaling, "quorum sensing", which is important for biofilm formation (Tateda *et al.*, 2004; Wozniak and Keyser, 2004). A combination of clarithromycin with cephazolin or vancomycin has also been shown to destroy *S. aureus* biofilms on titanium medical devices *in vitro*, although it was ineffective by itself (Fujimura *et al.*, 2008). This is a potentially promising area of research.

Coronary artery disease

Macrolides have been suggested to play a protective role against coronary artery disease, as a result of an antichlamydial or an antiinflammatory effect on atheromata. Initial studies with clarithromycin for this indication demonstrated contradictory results (Sinisalo *et al.*, 2002; Berg *et al.*, 2003; Berg *et al.*, 2003; Berg *et al.*, 2005; Peeters *et al.*, 2005). A recent large trial, enrolling about 2200 patients in each arm, showed a significantly increased relative risk of

death for those receiving clarithromycin compared with those receiving placebo (Gluud *et al.*, 2008). Together with the other randomized trials on antibiotics for patients with coronary heart disease versus placebo/no intervention (17 trials, 25,271 patients), these data argue against the systematic use of antibiotic in this indication.

Crohn's disease

Mycobacterium avium subspecies *paratuberculosis* has been suggested as a cause of Crohn's disease, and hence clarithromycin has been proposed to have a role in its treatment. However, there has been no support for this from clinical trials. One recent randomized controlled placebo trial used a combination of clarithromycin 750 mg daily, rifabutin 450 mg daily, and clofazimine 50 mg daily, as well as prednisolone, for an initial 16 weeks in 213 patients with active Crohn's disease. At this time, 66% in the antibiotic arm were in remission compared with 50% in the placebo arm ($p = 0.02$). A total of 122 patients in remission then received another 16 months of therapy. There was no substained benefit at 36 months (59% in antibiotic arm *vs* 50% placebo arm relapsed at one year; $p = 0.54$; Selby *et al.*, 2007). Another randomized placebo controlled–trial used clarithromycin alone (Leiper *et al.*, 2008). Patients were excluded if they were receiving 10 mg prednisolone or its equivalent daily. This trial was stopped after 41 patients were recruited because of poor efficacy. At three months there was no difference between the clarithromycin and placebo groups in combined remission or response rates; 26% (5/19) and 27% (6/22), respectively ($p = 1.00$).

Other

A randomized placebo-controlled trial of clarithromycin 500 mg in early rheumatoid arthritis showed promising results at six months (Ogrendik, 2007). Clarithromycin has also been used to treat Waldenstrom's macroglobulinemia (Coleman *et al.*, 2003; Dimopoulos *et al.*, 2003).

7k. Other uses

Like erythromycin, clarithromycin stimulates gastrointestinal and esophageal motility (Bortolotti *et al.*, 2000; Bortolotti *et al.*, 2006), and may have potential therapeutic applications in this area.

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